

09/210995

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FILE COVERS 1967 - 25 Mar 1999 VOL 130 ISS 13  
FILE LAST UPDATED: 25 Mar 1999 (19990325/ED)

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-key Terms

L1 ( 5032)SEA FILE=CAPLUS ABB=ON PLU=ON (HEMOPHIL? OR HAEMOPHIL?  
OR H) (W) INFLUENZ? OR NTHI OR OTITIS MEDIA  
L2 ( 55)SEA FILE=CAPLUS ABB=ON PLU=ON L1 AND ((HMW OR HMP) (S) MO  
LECU? OR HIGH(1W) (WEIGHT OR WT))  
L3 28 SEA FILE=CAPLUS ABB=ON PLU=ON L2 AND (ANTIGEN OR  
ADHESIN OR HNI47 OR HNI 47 OR HSP OR HEAT(W) SHOCK)

=> d 1-28 .beverly

L3 ANSWER 1 OF 28 CAPLUS COPYRIGHT 1999 ACS  
AN 1999:75537 CAPLUS  
TI A putative **adhesin** gene cloned from *Campylobacter jejuni*  
SO Res. Microbiol. (1998), 149(10), 723-733  
CODEN: RMCREW; ISSN: 0923-2508  
AU Kelle, K.; Pages, J.-M.; Bolla, J.-M.  
PY 1998  
AB Thirteen *Campylobacter jejuni* strains of human origin showed differing behaviors when analyzed for their ability to bind the Caco-2 cell line in vitro, suggesting variations in genetic complements and/or regulation. We designed an oligonucleotide probe corresponding to a highly conserved part of **adhesins** from various Gram-neg. bacteria. Among our lab. collection, Southern hybridization has demonstrated that only a discrete no. of strains harbor this sequence. The corresponding gene has been cloned from our prototype strain and sequence anal. has confirmed homol. with Gram-neg. bacterial **adhesins**. The ORF corresponded to 869 amino acids; we named this protein P95. Protein sequence similarity

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assessment demonstrated that this gene product belongs to the family of proteins including the filamentous haemagglutinin of Bordetella pertussis and the high-mol.-wt. surface-exposed adhesins of Haemophilus influenzae.

Comparison of adhesion and hybridization results emphasized the involvement of this gene in an essential pathogenic process of Campylobacter.

L3 ANSWER 2 OF 28 CAPLUS COPYRIGHT 1999 ACS

AN 1999:25012 CAPLUS

TI Characterization of emb, a gene encoding the major adhesin of Streptococcus defectivus

SO Infect. Immun. (1999), 67(1), 50-56

CODEN: INFIBR; ISSN: 0019-9567

AU Manganelli, Riccardo; Van De Rijn, Ivo

PY 1999

AB Streptococcus defectivus is one of the nutritionally variant streptococci, a class of viridans group streptococci first isolated from patients with endocarditis and otitis media. In previous studies, NVS-47, a clin. isolate of S. defectivus, was shown to bind to the extracellular matrix. A high-mol.-wt. surface protein was identified and proposed to be responsible for mediating this binding. In the present study, the gene encoding this protein was identified by transposon mutagenesis and characterized. The gene (emb) was found to be larger than 14 kb and was partially sequenced. It encodes a protein contg. at least 50 repeats of 77 amino acids predicted to assume an alternating coiled-coil conformation. The domain responsible for extracellular matrix binding was mapped to the N terminus of the protein. From sequence anal., Emb is proposed to be the prototype of a new family of streptococcal fibrillar proteins.

L3 ANSWER 3 OF 28 CAPLUS COPYRIGHT 1999 ACS

AN 1998:604694 CAPLUS

DN 129:242430

TI A high molecular weight major outer membrane protein of Moraxella and the gene encoding it

SO U.S., 34 pp. Cont.-in-part of U.S. Ser. No. 431,718.

CODEN: USXXAM

IN Sasaki, Ken; Harkness, Robin E.; Loosmore, Sheena M.; Klein, Michel H.

APPLICATION NO. DATE

AI	US 95-478370	19950607
	WO 96-CA264	19960429
	CA 96-2219889	19960429
	AU 96-53941	19960429
	EP 96-910872	19960429
	JP 96-532876	19960429

Searcher : Shears 308-4994

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	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5808024	A	19980915	US 95-478370	19950607
	WO 9634960	A1	19961107	WO 96-CA264	19960429
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	CA 2219889	AA	19961107	CA 96-2219889	19960429
	AU 9653941	A1	19961121	AU 96-53941	19960429
	EP 826052	A1	19980304	EP 96-910872	19960429
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 11502415	T2	19990302	JP 96-532876	19960429
PY	1998				
	1996				
	1996				
	1996				
	1998				
	1999				
AB	<p>An outer membrane protein of <i>Moraxella</i> strain, particularly <i>M. catarrhalis</i>, with a mol. mass of about 200,000 is characterized and the gene encoding it is cloned. The protein and the gene encoding it are useful in diagnostic applications and in vaccines against <i>Moraxella</i> infections, e.g. against <b>otitis media</b> and lower respiratory tract infections. The protein was identified as one present in clumping strains of <i>M. catarrhalis</i> but absent from non-clumping ones. Patients recovering from <b>otitis media</b> had antibodies to the protein. The protein was partially purified by gel electrophoresis and antibodies raised against it. The antibodies were used to screen a <i>Sau3A</i> partial digest expression library to obtain the gene.</p>				
L3	ANSWER 4 OF 28 CAPLUS COPYRIGHT 1999 ACS				
AN	1998:296924 CAPLUS				
DN	129:39889				
TI	Nasopharyngeal colonization with nontypeable <b>Haemophilus influenzae</b> in chinchillas				
SO	Infect. Immun. (1998), 66(5), 1973-1980 CODEN: INFIBR; ISSN: 0019-9567				
AU	Yang, Yan-Ping; Loosmore, Sheena M.; Underdown, Brian J.; Klein, Michel H.				
PY	1998				
AB	<p>Colonization of the nasopharynx by a middle ear pathogen is the first step in the development of <b>otitis media</b> in humans. The establishment of an animal model of nasopharyngeal</p> <p>Searcher : Shears 308-4994</p>				

colonization would therefore be of great utility in assessing the potential protective ability of candidate vaccine antigens (esp. adhesins) against otitis media.

A chinchilla nasopharyngeal colonization model for nontypeable *Haemophilus influenzae* (NTHI) was developed with antibiotic-resistant strains. This model does not require coinfection with a virus. There was no significant difference in the efficiency of NTHI colonization between adult (1- to 2-yr-old) and young (2- to 3-mo-old) animals. However, the incidence of middle ear infection following nasopharyngeal colonization was significantly higher in young animals (83 to 89%) than in adult chinchillas (10 to 30%). Chinchillas that had recovered either from a previous middle ear infection caused by NTHI or from an infection by intranasal inoculation with NTHI were completely protected against nasopharyngeal colonization with a homologous strain and were the best pos. controls in protection studies. Systemic immunization of chinchillas with inactivated whole-cell preps. significantly protected animals not only against homologous NTHI colonization but also partially against heterologous NTHI infection. In all protected animals, significant serum anti-P6 and anti-HMW antibody responses were obsd. The outer membrane P6 and high-mol.-wt. (HMW) proteins appear to be promising candidate vaccine antigens to prevent nasopharyngeal colonization and middle ear infection caused by NTHI.

L3 ANSWER 5 OF 28 CAPLUS COPYRIGHT 1999 ACS

AN 1998:296912 CAPLUS

DN 129:53186

TI Synthesis and characterization of lipooligosaccharide-based conjugates as vaccine candidates for *Moraxella* (*Branhamella*) *catarrhalis*

SO Infect. Immun. (1998), 66(5), 1891-1897  
CODEN: INFIBR; ISSN: 0019-9567

AU Gu, Xin-Xing; Chen, Jing; Barenkamp, Stephen J.; Robbins, John B.; Tsai, Chao-Ming; Lim, David J.; Battey, James

PY 1998

AB *Moraxella* (*Branhamella*) *catarrhalis* is an important cause of otitis media and sinusitis in children and of lower respiratory tract infections in adults. Lipooligosaccharide (LOS) is a major surface antigen of the bacterium and elicits bactericidal antibodies. Treatment of the LOS from strain ATCC 25238 with anhyd. hydrazine reduced its toxicity 20,000-fold, as assayed in the *Limulus* amebocyte lysate (LAL) test. The detoxified LOS (dLOS) was coupled to tetanus toxoid (TT) or high-mol.-wt. proteins (HMP) from nontypeable *Haemophilus influenzae* through a linker of adipic acid dihydrazide to form dLOS-TT or dLOS-

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**HMP.** The molar ratios of dLOS to TT and HMP conjugates were 19:1 and 31:1, resp. The antigenicity of the two conjugates was similar to that of the LOS, as detd. by double immunodiffusion. S.c. or i.m. injection of both conjugates elicited a 50- to 100-fold rise in the geometric mean of IgG to the homologous LOS in mice after three injections and a 350- to 700-fold rise of anti-LOS IgG in rabbits after two injections. The immunogenicity of the conjugate was enhanced by formulation with monophosphoryl lipid A plus trehalose dimycolate. In rabbits, conjugate-induced antisera had complement-mediated bactericidal activity against the homologous strain and heterologous strains of *M. catarrhalis*. These results indicate that a detoxified LOS-protein conjugate is a candidate for immunization against *M. catarrhalis* diseases.

L3 ANSWER 6 OF 28 CAPLUS COPYRIGHT 1999 ACS  
 AN 1998:7848 CAPLUS  
 DN 128:138477  
 TI Prevalence and distribution of the hmw and hia genes and the HMW and Hia adhesins among genetically diverse strains of nontypeable *Haemophilus influenzae*  
 SO Infect. Immun. (1998), 66(1), 364-368  
 CODEN: INFIBR; ISSN: 0019-9567  
 AU St. Geme, Joseph W., III; Kumar, Vini V.; Cutter, David; Barenkamp, Stephen J.  
 PY 1998  
 AB Nontypeable *Haemophilus influenzae* is a common cause of human disease and initiates infection by colonizing the upper respiratory tract. In previous work we identified high-mol.-wt. adhesins referred to as HMW1 and HMW2, expressed by nontypeable strain 12, and detd. that most strains of nontypeable *H. influenzae* express one or two antigenically related proteins. More recently, we detd. that some strains lack HMW1- and HMW2-like proteins and instead express an adhesin called Hia. In the present study, we detd. the prevalence and distribution of the hmw and hia genes in a collection of 59 nontypeable strains previously characterized in terms of genetic relatedness. Based on Southern anal., 47 strains contained sequences homologous to the hmw1 and hmw2 genes and nine strains contained homologs to hia. No strain harbored both hmw and hia, and three strains harbored neither. Although the hmw and hia genes failed to define distinct genetic divisions, the hmw-deficient strains formed small clusters or lineages within the larger population structure. Addnl. anal. established that the IS1016 insertion element was uniformly absent from strains contg. hmw sequences but was present in two-thirds of the hmw-deficient strains. As IS1016 is assocd. with the capsule locus (cap) in most encapsulated strains of *H. influenzae*, we speculate that hmw-deficient nontypeable strains evolved more recently from an encapsulated ancestor.

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L3 ANSWER 7 OF 28 CAPLUS COPYRIGHT 1999 ACS

AN 1997:679100 CAPLUS

DN 127:345324

TI High molecular weight surface proteins of  
non-typeable Haemophilus

SO PCT Int. Appl., 182 pp.

CODEN: PIXXD2

IN Barenkamp, Stephen J.

APPLICATION NO. DATE

AI WO 97-US4707 19970401

AU 97-25873 19970401

EP 97-917597 19970401

PATENT NO. KIND DATE

APPLICATION NO. DATE

PI WO 9736914 A1 19971009 WO 97-US4707 19970401

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,  
DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP,  
KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,  
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT,  
UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR,  
GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM,  
GA, GN, ML, MR, NE, SN, TD, TG

AU 9725873 A1 19971022 AU 97-25873 19970401

EP 900232 A1 19990310 EP 97-917597 19970401

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC,  
PT, IE, FI

PY 1997

1997

1999

AB High mol. wt. surface proteins of non-typeable  
Haemophilus influenzae which exhibit immunogenic  
properties and genes encoding the same are described. Specifically,  
genes coding for two immunodominant high mol. wt  
. proteins, HMW1 and HMW2, have been cloned, expressed and  
sequenced, while genes coding for high mol. proteins HMW3 and HMW4  
have also been cloned, expressed and sequenced. These proteins,  
epitopes, or conjugates with other antigen, hapten, or  
polysaccharide are useful for eliciting immune response to protect  
against Haemophilus influenza type b.

L3 ANSWER 8 OF 28 CAPLUS COPYRIGHT 1999 ACS

AN 1997:69841 CAPLUS

DN 126:94782

TI Vaccine composition containing polyribosylribitol phosphate and  
method for making same

SO PCT Int. Appl., 21 pp.

Searcher : Shears 308-4994

09/210995

IN CODEN: PIXXD2  
Arminjon, Francois; Cartier, Jean-Rene  
APPLICATION NO. DATE

AI WO 96-FR791 19960524  
FR 95-6417 19950524  
CA 96-2218764 19960524  
AU 96-60086 19960524  
EP 96-917554 19960524  
CN 96-195582 19960524  
NO 97-5366 19971121  
PATENT NO. KIND DATE

APPLICATION NO. DATE

PI WO 9637222 A1 19961128 WO 96-FR791 19960524  
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK,  
EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR,  
LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO,  
RU, SD, SE, SG, SI  
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB,  
GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,  
GN  
FR 2734484 A1 19961129 FR 95-6417 19950524  
FR 2734484 B1 19970627  
CA 2218764 AA 19961128 CA 96-2218764 19960524  
AU 9660086 A1 19961211 AU 96-60086 19960524  
EP 828511 A1 19980318 EP 96-917554 19960524  
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT,  
IE, FI  
CN 1190898 A 19980819 CN 96-195582 19960524  
NO 9705366 A 19971121 NO 97-5366 19971121

PY 1996  
1996  
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1997

AB A vaccine compn. contg. 1 or more antigens comprising the  
high mol. wt. capsular polysaccharide of the type  
b *Haemophilus influenza*, or polyribosylribitol  
phosphate, coupled to the tetanus toxoid and an aluminum-based  
adjuvant, wherein the aluminum-based adjuvant has, in its natural  
state, or following anion addn., a zero point of charge of <7.2. A  
method for making the vaccine compn. is also described. A vaccine  
compn. contained aluminum hydroxide 0.25 mg, PRP-T 10 .mu.g, ADP and  
ATP 1 vaccinating dose each, phosphates 15 .mu.mol, polio  
antigen type I, II, and III 40, 8, and 32 U resp., pertussis  
toxin 25 .mu.g, buffer 0.125 mL, and water 0.5 mL.

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L3 ANSWER 9 OF 28 CAPLUS COPYRIGHT 1999 ACS  
 AN 1996:606388 CAPLUS  
 DN 125:245149  
 TI Synthesis, characterization, and immunologic properties of  
 detoxified lipooligosaccharide from nontypeable *Haemophilus*  
*influenzae* conjugated to proteins  
 SO Infect. Immun. (1996), 64(10), 4047-4053  
 CODEN: INFIBR; ISSN: 0019-9567  
 AU Gu, Xin-Xing; Tsai, Chao-Ming; Ueyama, Tomoyo; Barenkamp, Stephen  
 J.; Robbins, John B.; Lim, David J.  
 PY 1996  
 AB Nontypeable *Haemophilus influenzae* (NTHi  
 ) is an important cause of otitis media in  
 children and of pneumonitis in adults with depressed resistance.  
 Lipooligosaccharide (LOS) is a major surface antigen of  
 NTHi and elicits bactericidal and opsonic antibodies. We  
 prepd. detoxified LOS (dLOS) protein conjugates from NTHi  
 for use as exptl. vaccines. LOS from NTHi 9274 was  
 treated with anhyd. hydrazine and had its toxicity reduced to clin.  
 acceptable levels. DLOS was bound to tetanus toxoid (TT) or  
 high-mol.-wt. proteins (HMPs)  
 from NTHi through a linker of adipic acid dihydrazide to  
 form dLOS-TT or dLOS-HMP. The molar ratio of the dLOS to  
 protein carriers ranged from 26:1 to 50:1. The antigenicity of the  
 conjugates was similar to that of the LOS alone as detd. by double  
 immunodiffusion. S.c. or i.m. injection of the conjugates elicited  
 a 28- to 486-fold rise in the level of IgG antibodies in mice to the  
 homologous LOS after two or three injections and a 169- to 243-fold  
 rise in the level of IgG antibodies in rabbits after two injections.  
 The immunogenicity of the conjugates in mice and rabbits was  
 enhanced by formulation with monophosphoryl lipid A plus trehalose  
 dimycolate. In rabbits, conjugate-induced LOS antibodies induced  
 complement-mediated bactericidal activity against the homologous  
 strain 9274 and prototype strain 3189. These results indicate that  
 a detoxified LOS-protein conjugate is a candidate vaccine for  
 otitis media and pneumonitis caused by  
 NTHi.

L3 ANSWER 10 OF 28 CAPLUS COPYRIGHT 1999 ACS  
 AN 1996:455154 CAPLUS  
 DN 125:139983  
 TI Identification of surface-exposed B-cell epitopes on high  
 -molecular-weight adhesion proteins of nontypeable  
*Haemophilus influenzae*  
 SO Infect. Immun. (1996), 64(8), 3032-3037  
 CODEN: INFIBR; ISSN: 0019-9567  
 AU Barenkamp, Stephen J.; St. Geme, Joseph W., III  
 PY 1996

Searcher : Shears 308-4994



AB Two surface-exposed high-mol.-wt. proteins, HMW1 and HMW2, expressed by a prototypic strain of nontypeable H . influenzae (NTHI) mediate attachment to human epithelial cells. These proteins are members of a family of highly immunogenic proteins common to most nontypeable Haemophilus strains. Immunization with an HMW1-HMW2 mixt. modified the course of disease in an animal model of otitis media, suggesting the potential usefulness of these proteins as NTHI vaccine components. Identification of surface-accessible B-cell epitopes could be important to efforts to develop recombinant or synthetic peptide vaccines based upon these high-mol.-wt. proteins. The purpose here was to identify surface-accessible epitopes on the HMW1 and HMW2 proteins by using monoclonal antibodies (MAbs) and to det. the prevalence of these epitopes among the high-mol.-wt. proteins expressed by heterologous nontypeable Haemophilus strains. MAbs were generated by immunizing mice with high-mol.-wt. proteins purified from prototype strains and were screened by immunoelectron microscopy (IEM) for the ability to recognize surface epitopes. Two MAbs, designated AD6 and 10C5, that recognized surface epitopes by IEM were recovered. To map the epitopes recognized by these 2 MAbs, a set of HMW1 and HMW2 recombinant fusion proteins was constructed using the pGEMEX vectors and the reactivity of the MAbs with these fusion proteins was examd. MAb AD6 recognized an epitope in both HMW1 and HMW2 which mapped to the last 75 amino acids at the C termini of the 2 proteins. When examd. for reactivity with heterologous strains, MAb AD6 recognized high-mol.-wt. proteins in 75% of 125 unrelated nontypeable Haemophilus strains and, in addn., reacted with 3 of 3 such strains when examd. by IEM. MAb 10C5 recognized an epitope that mapped to a 155-amino-acid segment near the C terminus of HMW1. This epitope was adjacent to but distinct from the AD6 epitope and was absent from HMW2. The 10C5 epitope was expressed by 40% of the AD6 reactive strains. Identification of shared surface-exposed epitopes on the high-mol.-wt. adhesion proteins suggests the possibility of developing recombinant or synthetic peptide-based vaccines protective against disease caused by the majority of NTHI strains.

L3 ANSWER 11 OF 28 CAPLUS COPYRIGHT 1999 ACS  
 AN 1996:327952 CAPLUS  
 DN 125:7851  
 TI Evaluation of purified UspA from Moraxella catarrhalis as a vaccine in a murine model after active immunization  
 SO Infect. Immun. (1996), 64(6), 1900-1905  
 CODEN: INFIBR; ISSN: 0019-9567  
 AU Chen, Dexiang; McMichael, John C.; VanDerMeid, Karl R.; Hahn, Denise; Mininni, Terri; Cowell, James; Eldridge, John  
 PY 1996

Searcher : Shears 308-4994

AB *Moraxella catarrhalis* causes otitis media, laryngitis, and respiratory infections in humans. A high-mol.-wt. outer membrane protein from this bacterium named ubiquitous surface protein A (UspA) is present on all isolates. A monoclonal antibody (MAb) to UspA that recognizes a conserved epitope of this protein has been shown to promote pulmonary clearance of bacteria in passively immunized. In the present study, *M. catarrhalis* heterologous isolates were screened by dot blot with a panel of 4 addnl. MAb specific for surface-exposed epitopes of UspA from *M. catarrhalis* isolate O35E. Three of the MAb were specific for O35E, and the 4th reacted with 17 (74%) of the 23 isolates tested. Thus, UspA contains highly conserved, semiconserved, and variable surface-exposed epitopes. The UspA was purified from the O35E isolate by ion-exchange and size-exclusion chromatog., formulated with the adjuvant QS-21, and used to immunize BALB/c mice. Upon pulmonary challenge with either O35E or the heterologous isolate TTA24, significantly fewer bacteria were recovered from the lungs of immunized mice 6 h postchallenge than from control mice. The immune sera from mice or guinea pigs contained high titers of antibodies to the homologous isolate and heterologous isolates in a whole-bacterial-cell ELISA. Sera against UspA, whether prepd. in mice or guinea pigs, had complement-dependent bactericidal activity toward homologous and 11 heterologous *M. catarrhalis* isolates. These results indicate that the conserved epitopes of the UspA are highly immunogenic and elicit broadly reactive and biol. functional antibodies. UspA may offer protection against *M. catarrhalis* infections and is being further evaluated as a vaccine candidate.

L3 ANSWER 12 OF 28 CAPLUS COPYRIGHT 1999 ACS

AN 1996:213484 CAPLUS

DN 124:255432

TI Identification of a second family of high-molecular-weight adhesion proteins expressed by non-typable *Haemophilus influenzae*

SO Mol. Microbiol. (1996), 19(6), 1215-23

CODEN: MOMIEE; ISSN: 0950-382X

AU Barenkamp, Stephen J.; St. Geme, Joseph W., III

PY 1996

AB We previously reported that two surface-exposed high-mol.-wt. proteins, HMW1 and HMW2, expressed by a prototypic strain of non-typable *Haemophilus influenzae* (NTHI), mediate attachment to human epithelial cells. These proteins are members of a family of highly immunogenic proteins common to 70-75% of NTHI strains. NTHI strains that lack HMW1/HMW2-like proteins remain capable of efficient attachment to cultured human epithelial cells, suggesting the existence of addnl. adhesion mols. We reasoned that characterization of high-mol.-wt. immunogenic

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proteins from an HMW1/HMW2-deficient strain might identify adnl. adhesion proteins. A genomic library was prepd. in .lambda.EMBL3 with chromosomal DNA from non-typable *Haemophilus* strain 11, a strain that lacks HMW1/HMW2-like proteins. The library was screened immunol. with convalescent serum from a child naturally infected with strain 11, and phage clones expressing high-mol.-wt. recombinant proteins were identified by Western blot anal. One clone was identified that expressed a protein with an apparent mol. mass greater than 200 kDa. Transformation of non-adherent *Escherichia coli* strain DH5.alpha. with plasmids contg. the genetic locus encoding this protein gave rise to *E. coli* transformants that adhered avidly to Chang conjunctival cells. Subcloning and mutagenesis studies localized the DNA conferring the adherence phenotype to a 4.8 kbp fragment, and nucleotide sequence anal. further localized the gene encoding the adhesion protein to a 3.3 kbp open reading frame predicted to encode a protein of 114 kDa. The gene was designated *hia* for *Haemophilus influenzae* adhesin. Southern anal. revealed an *hia* homolog in 13 of 15 HMW1/HMW2-deficient non-typable *H. influenzae* strains. In contrast, the *hia* gene was not present in any of 23 non-typable *H. influenzae* strains which expressed HMW1/HMW2-like proteins. Identification of this second family of high-mol.-wt. adhesion proteins suggests the possibility of developing vaccines based upon a combination of HMW1/HMW2-like proteins and *Hia*-like proteins which would be protective against disease caused by most of all non-typable *H. influenzae*.

L3 ANSWER 13 OF 28 CAPLUS COPYRIGHT 1999 ACS

AN 1996:190693 CAPLUS

DN 124:229356

TI Immunization with high-molecular-weight adhesion proteins of nontypeable *Haemophilus influenzae* modifies experimental otitis media in chinchillas

SO Infect. Immun. (1996), 64(4), 1246-51  
CODEN: INFIBR; ISSN: 0019-9567

AU Barenkamp, Stephen J.

PY 1996

AB Prevention of nontypeable *Haemophilus influenzae* otitis media by vaccination is an important health care goal. Proteins important in bacterial adherence deserve consideration as potential vaccine candidates. Two colleagues and I previously identified a family of immunogenic high-mol.-wt. proteins important in adherence to nontypeable *H. influenzae* to human epithelial cells (J. W. St. Geme III, S. Falkow, and S. J. Barenkamp, Proc. Natl. Acad. Sci. USA, 90:2875-2879, 1993). In the work described here, I detd. whether immunization with two such adherence proteins, HMW1 and HMW2,

Searcher : Shears 308-4994

purified from prototype nontypeable *Haemophilus* strain 12, would modify the course of exptl. otitis media caused by the homologous strain. Chinchillas received three monthly s.c. injections with 40 .mu.g of a HMW1/HMW2 protein mixt. in Freund's adjuvant. One month after the last injection, animals were challenged by intrabullar inoculation with 300 CFU of nontypeable *H. influenzae* 12. Infection developed in five of five control animals vs. 5 of 10 immunized animals ( $P = 0.08$ , Fisher exact, one-tailed). Among infected animals, bacterial counts in middle ear fluid specimens 7 days postchallenge were significantly greater in control animals than in immunized animals ( $P = 0.014$ , Mann-Whitney U test). Serum antibody titers following immunization were comparable in uninfected and infected animals. However, infection in immunized animals was uniformly assocd. with the appearance of bacteria downregulated in expression of the high-mol.-wt. proteins, suggesting bacterial selection in response to immunol. pressure. Although protection following immunization was incomplete, these data suggest that the high-mol.-wt. adhesion proteins are potentially important protective antigens which might represent one component of a multicomponent nontypeable *Haemophilus* vaccine.

L3 ANSWER 14 OF 28 CAPLUS COPYRIGHT 1999 ACS  
 AN 1995:1006690 CAPLUS  
 DN 124:28122  
 TI Preparation of antigen from fermentation broth  
 SO Jpn. Kokai Tokkyo Koho, 12 pp.  
 CODEN: JKXXAF

IN Nishida, Yasukuni

APPLICATION NO. DATE

AI	JP 94-98059	19940412		
	PATENT NO.	KIND	DATE	APPLICATION NO. DATE
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PI	JP 07274993	A2	19951024	JP 94-98059 19940412
PY	1995			

AB Fermn. broth of a microorganism is subjected to removal of high mol.-wt. substances, and used for further culture of the microorganism to prep. antigen in the culture supernatant. The method gives high yield and is simple. The antigen thus prepd. is useful for induction of antibodies. Prepn. of antigen of *Streptococcus pyogenes* by subjecting the fermn. broth to ultrafiltration to remove the high mol.-wt. substances was shown.

L3 ANSWER 15 OF 28 CAPLUS COPYRIGHT 1999 ACS  
 AN 1995:659115 CAPLUS  
 DN 123:109185  
 TI Binding of *Haemophilus influenzae* to purified  
 Searcher : Shears 308-4994

- mucins from the human respiratory tract
- SO Infect. Immun. (1995), 63(7), 2485-92  
CODEN: INFIBR; ISSN: 0019-9567
- AU Davies, Julia; Carlstedt, Ingemar; Nilsson, Ann-Kristin; Hakansson, Anders; Sabharwal, Hemant; Van Alphen, Loek; Van Ham, Marieke; Svanborg, Catharina
- PY 1995
- AB Mucins are high-mol.-wt. glycoproteins and major constituents of the mucus layer which covers the airway surface. The authors have studied the interactions between bacteria, mucins, and epithelial cells from the human respiratory tract. Non-typeable strains of *Haemophilus influenzae* bound purified airway mucins in suspension and on solid phase. Mucins in suspension inhibited the attachment of these strains to nasopharyngeal epithelial cells, while mucin coating of the cells enhanced their binding. In contrast, strains of *Streptococcus pneumoniae* and encapsulated and other non-typeable *H. influenzae* strains failed to interact with mucins. These *H. influenzae* strains used other strategies for adherence to epithelial cells. The type b strain 770235 attached via fimbriae but also expressed a subcapsular adhesin that was detected in a capsule- and fimbria-defective mutant. Mucin pretreatment of these bacteria did not inhibit adherence, but mucin pretreatment of epithelial cells inhibited adherence, probably by shielding of the receptors for these adhesins. Non-mucin-binding non-typeable and encapsulated *H. influenzae* strains would, therefore, adhere only after disruption of the mucus layer and exposure of cellular receptors. Differences in tissue toxicity and invasiveness among *H. influenzae* strains may also be influenced by the mucin interactions of the strains.
- L3 ANSWER 16 OF 28 CAPLUS COPYRIGHT 1999 ACS
- AN 1994:696730 CAPLUS
- DN 121:296730
- TI Localization of high-molecular-weight adhesion proteins of nontypeable *Haemophilus influenzae* by immunoelectron microscopy
- SO Infect. Immun. (1994), 62(10), 4460-8  
CODEN: INFIBR; ISSN: 0019-9567
- AU Bakaletz, L. O.; Barenkamp, S. J.
- PY 1994
- AB A family of high-mol.-wt. (HMW)  
) surface-exposed proteins important in the attachment of nontypeable *Haemophilus influenzae* (NTHi)  
) to humans epithelial cells was previously identified (J. W. St. Geme III, S. Falkow, and S. J. Barenkamp, Proc. Natl. Acad. Sci. USA 90:2875-2879, 1993). In the present investigation, indirect immunogold labeling and electron microscopy were used to localize
- Searcher : Shears 308-4994

these proteins on three clin. isolates of *NTHi*, mutants deficient in expression of one or both HMW proteins, and embedded sections of human oropharyngeal cells after incubation with *NTHi* strain 12. The filamentous material comprising the proteins was labeled with monoclonal antibodies directed against two prototype HMW proteins (HMW1 and HMW2) of prototype *NTHi* strain 12. Gold labeling was obsd. as a cap or discrete aggregate off one pole or centrally along one long axis of the bacterial cell. Heavily labeled, non-bacterial-cell-assocd., disk-like aggregates of the HMW proteins were frequently noted in both bacterial preps. as well as in assocn. with the oropharyngeal cell surface and intracellularly. Mutants demonstrated diminished labeling or an absence thereof, resp., which correlated well with their previously demonstrated reduced ability or inability to adhere to Chang conjunctival epithelial cells in vitro. The *Haemophilus* HMW proteins share antigenic determinants with and demonstrate amino acid sequence similarity to the filamentous hemagglutinin protein of *Bordetella pertussis*, a crit. adhesin of that organism. The studies presented here demonstrate that the *Haemophilus* proteins and *B. pertussis* filamentous hemagglutinin show impressive morphol. and perhaps addnl. functional similarity.

L3 ANSWER 17 OF 28 CAPLUS COPYRIGHT 1999 ACS

AN 1994:576469 CAPLUS

DN 121:176469

TI The HMW1 adhesin of nontypeable *Haemophilus influenzae* recognizes sialylated glycoprotein receptors on cultured human epithelial cells

SO Infect. Immun. (1994), 62(9), 3881-9

CODEN: INFIBR; ISSN: 0019-9567

AU St. Geme, Joseph W., III

PY 1994

AB Disease due to nontypeable *H. influenzae* begins with colonization of the upper respiratory tract mucosa. The authors recently reported that two surface-exposed high-mol.-wt. proteins (HMW1 and HMW2) expressed by a prototypic strain of nontypeable *H. influenzae* mediate attachment to cultured epithelial cells. In the present study, the authors examd. the nature of the epithelial cells receptor with which HMW1 interacts. Both proteinase K pretreatment and periodate oxidn. of epithelial monolayers resulted in a marked decrease in HMW1-mediated binding, suggesting interaction with a glycoprotein structure. Treatment with peptide-N-glycosidase F produced a similar decrease in attachment and thereby provided further evidence for this conclusion. Desialylation of the epithelial cell surface also reduced binding, implying the presence of sialic acid were capable of inhibiting HMW1-mediated attachment. In summary, these results indicate that the HMW1 adhesin interacts with a glycoprotein receptor contg. N-linked

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oligosaccharide chains with sialic acid in an .alpha.2-3 configuration.

L3 ANSWER 18 OF 28 CAPLUS COPYRIGHT 1999 ACS  
AN 1994:268066 CAPLUS  
DN 120:268066  
TI High-molecular-weight surface-exposed proteins  
of *Haemophilus influenzae* mediate binding to  
macrophages  
SO J. Infect. Dis. (1994), 169(2), 425-9  
CODEN: JIDIAQ; ISSN: 0022-1899  
AU Noel, Gary J.; Barenkamp, Stephen J.; St. Geme, Joseph W. III;  
Haining, W. Nicholas; Mosser, David M.  
PY 1994  
AB The mol. basis for direct bacteria-macrophage interactions that  
distinguishes nontypeable (NT) *Haemophilus*  
*influenzae* from type b organisms is not known. Because of  
similarities between filamentous hemagglutinin (FHA) adhesin  
of *Bordetella pertussis* and high-mol.-wt  
(HMW) proteins commonly expressed by NT H.  
*influenzae*, the role that HMW proteins play in  
detg. NT H. *influenzae*-macrophage interactions  
was assessed. In tests with genetically engineered organisms, HMW  
protein-expressing bacteria bound significantly better than isogenic  
HMW protein-deficient bacteria to macrophages. HMW  
protein-dependent binding to macrophages is trypsin-sensitive, is  
independent of divalent cations, does not occur via the leukocyte  
integrin CD11b/CD18, and is not affected by galactose-contg.  
carbohydrates. Organisms bound via HMW proteins remain largely  
extracellular and viable. Like FHA of *Bordetella* organisms, HMW  
proteins mediate binding of NT H. *influenzae* to  
macrophages. However, unlike the interaction detd. by FHA, this  
interaction is characteristically one of adhesion and requires  
addnl. serum opsonization for efficient killing of bacteria by  
macrophages.

L3 ANSWER 19 OF 28 CAPLUS COPYRIGHT 1999 ACS  
AN 1994:212212 CAPLUS  
DN 120:212212  
TI Purification and characterization of a high-molecular-  
weight outer membrane protein of *Moraxella* (*Branhamella*)  
*catarrhalis*  
SO Infect. Immun. (1994), 62(4), 1150-5  
CODEN: INFIBR; ISSN: 0019-9567  
AU Klingman, Karin L.; Murphy, Timothy F.  
PY 1994  
AB *Moraxella* (*Branhamella*) *catarrhalis* is an important bacterial cause  
of otitis media in children and lower  
respiratory tract infections in adults. The authors describe the  
Searcher : Shears 308-4994

presence of a novel high-mol.-wt. outer membrane protein (HMW-OMP). This protein varies from 350 to 720 kDa in apparent mol. mass among strains by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). The protein was detected on SDS-PAGE in 13 of 14 strains tested. The authors developed a monoclonal antibody and polyclonal antisera to this protein. In immunoblot assays, the protein was present in all 14 strains tested. The immunoblot assays suggest that the protein has at least one epitope that is conserved among strains. A purifn. method using anion-exchange chromatog. is described. Treatment of outer membrane preps. and purified protein by heat and reducing agents did not change the apparent mol. mass of the HMW-OMP. Formic acid treatment of outer membrane preps. and purified HMW-OMP produced a single band with an apparent mol. mass of 120 to 140 kDa. The authors postulate that this may be the monomer of an oligomeric protein. The HMW-OMP, which varies in mol. mass among strains and is antigenically conserved, will be studied further to det. its role in the human immune response and may be useful as a marker in studying strain acquisition in patients.

L3 ANSWER 20 OF 28 CAPLUS COPYRIGHT 1999 ACS

AN 1994:2261 CAPLUS

DN 120:2261

TI Cloning and expression of high molecular weight surface proteins of non-typeable Haemophilus

SO PCT Int. Appl., 99 pp.

CODEN: PIXXD2

IN Barenkamp, Stephen J.

APPLICATION NO. DATE

AI	WO 93-US2166	19930316
	AU 93-39168	19930316
	EP 93-908295	19930316
	JP 93-516604	19930316
	BR 93-6109	19930316
	NO 94-3431	19940915
	FI 94-4273	19940915
	US 94-302832	19941005
	US 95-469880	19950606
	PATENT NO.	KIND DATE

APPLICATION NO. DATE

PI	WO 9319090	A1	19930930	WO 93-US2166 19930316
	W: AU, BR, CA, FI, JP, KR, NO, RU, UA, US			
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT,			
	SE			
	AU 9339168	A1	19931021	AU 93-39168 19930316
	AU 669360	B2	19960606	
	EP 632814	A1	19950111	EP 93-908295 19930316
	Searcher : Shears 308-4994			



09/210995

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL,  
PT, SE

JP 07506248	T2	19950713	JP 93-516604	19930316
BR 9306109	A	19971118	BR 93-6109	19930316
NO 9403431	A	19941110	NO 94-3431	19940915
FI 9404273	A	19941115	FI 94-4273	19940915
US 5603938	A	19970218	US 94-302832	19941005
US 5876733	A	19990302	US 95-469880	19950606

PY 1993  
1993  
1996  
1995  
1995  
1997  
1994  
1994  
1997  
1999

AB The genes for high mol. wt. surface proteins HMW1 and 2 of *H. influenzae* are cloned and sequenced. The amino acid sequences of HMW1 and 2 derived from the genes had high homol. with that of the filamentous hemagglutinin of *Bordetella pertussis*. The HMW1 and 2 are useful for prepn. of protective antigens against nontypeable *Haemophilus*-assocd. diseases such as otitis, sinusitis, bronchitis, etc., and as carrier for the protective Hib carrier polysaccharides in a conjugate vaccine against meningitis. The genes for the high mol. wt. surface proteins were cloned from a genomic library of *H. influenzae* constructed on .lambda.EMBL3 by immunol. screening using an human antibody against the high mol. wt. surface proteins. Also shown was the adherence of the HMW1 and 2 on the Chang epithelial cells. HMW3 and 4 were also cloned and partially sequenced.

L3 ANSWER 21 OF 28 CAPLUS COPYRIGHT 1999 ACS

AN 1993:206310 CAPLUS

DN 118:206310

TI Cloning, expression, and DNA sequence analysis of genes encoding nontypeable *Haemophilus influenzae* high

-molecular-weight surface-exposed proteins related to filamentous hemagglutinin in *Bordetella pertussis*

SO Infect. Immun. (1992), 60(4), 1302-13

CODEN: INFIBR; ISSN: 0019-9567

AU Barenkamp, Stephen J.; Leininger, Elizabeth

PY 1992

AB A group of high-mol.-wt. surface-exposed proteins of nontypeable *H. influenzae* are major targets of human serum antibody. To further characterize these proteins, genes encoding 2 related high-mol.-wt.

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proteins were cloned and sequenced from a prototype nontypeable *Haemophilus* strain. The gene encoding a 120-kDa *Haemophilus* protein consisted of a 4.4-kbp open reading frame, and the gene encoding a 125-kDa protein consisted of a 4.6-kbp open reading frame. The first 1259 bp of the 2 genes were identical. Thereafter, the sequences began to diverge, but overall they were 80% identical, and the derived amino acid sequences showed 70% identity. A protein sequence homol. search demonstrated similarity between the derived amino acid sequences of both cloned genes and the derived amino acid sequence of the gene encoding filamentous hemagglutinin, a surface protein produced by the gram-neg. pathogen *B. pertussis*. Antiserum raised against a recombinant protein encoded by the 4.6-kbp open reading frame recognized both the 120- and the 125-kDa proteins in the prototype strain as well as antigenically related high-mol.-wt. proteins in 75% of a collection of 125 epidemiol. unrelated nontypeable *H. influenzae* strains. The antiserum directed against the recombinant protein also recognized purified filamentous hemagglutinin. A murine monoclonal antibody to filamentous hemagglutinin recognized both the 120-kDa and the 125-kDa protein in the prototype strain as well as proteins identical to those recognized by the recombinant-protein antiserum in 35% of the nontypeable *H. influenzae* strain collection. Thus, the authors have identified and partially characterized a group of highly immunogenic surface-exposed proteins of nontypeable *H. influenzae* which are related to the filamentous hemagglutinin of *B. pertussis*.

L3 ANSWER 22 OF 28 CAPLUS COPYRIGHT 1999 ACS  
 AN 1990:495780 CAPLUS  
 DN 113:95780  
 TI Expression in *Escherichia coli* of a high-molecular-weight protective surface antigen found in nontypeable and type b *Haemophilus influenzae*  
 SO Infect. Immun. (1990), 58(6), 1909-13  
 CODEN: INFIBR; ISSN: 0019-9567  
 AU Thomas, W. R.; Callow, M. G.; Dilworth, R. J.; Audesho, A. A.  
 PY 1990  
 AB An *E. coli* clone producing a high-mol.-wt. surface antigen of *H. influenzae* type b (Hib) was isolated from a library of Hib DNA fragments cloned as lysogens in a lambda replacement vector. The antigen is found in sarcosyl-insol. outer membrane protein preps. and was produced by all 36 *H. influenzae* isolates tested. Absorption studies indicated that the antigen is a surface determinant on all isolates tested. Antibodies to the antigen (D15) were found in 8 of 9 convalescent-phase sera from children with invasive Hib infection. Affinity-purified antibodies prepd. against the cloned antigen gave protection against the development of bacteremia in a rat pup model.  
 Searcher : Shears 308-4994

L3 ANSWER 23 OF 28 CAPLUS COPYRIGHT 1999 ACS

AN 1987:573808 CAPLUS

DN 107:173808

TI **Haemophilus influenzae** type b  
lipooligosaccharide: stability of expression and association with virulence

SO Infect. Immun. (1987), 55(9), 1979-86

CODEN: INFIBR; ISSN: 0019-9567

AU Kimura, Alan; Patrick, Christian C.; Miller, Elizabeth E.; Cope, Leslie D.; McCracken, George H., Jr.; Hansen, Eric J.

PY 1987

AB Spontaneous antigenic and phenotypic variations in the lipooligosaccharide (LOS) of 2 strains of **H. influenzae** type b (Hib) were previously shown to be assocd. with changes in virulence (A. Kimura and E. J. Hansen, 1986). The goal of the present study was to define further the stability of LOS expression by this pathogen and the role of Hib LOS in virulence. Variation in LOS antigenic reactivity, as detected with LOS-specific-monoclonal antibodies, was obsd. in 3 of 30 Hib strains after single-colony passage. When large nos. of individual colonies from 7 other Hib strains were screened, however, spontaneous LOS antigenic variation was detected in all of the strains. Antigenic variation was not consistently assocd. with an altered LOS phenotype, as detd. by SDS-PAGE and Ag staining of LOS preps. Changes in the LOS antigenic phenotype were correlated with altered virulence potential in 2 strains. In these strains, acquisition of reactivity with certain LOS-directed monoclonal antibodies was assocd. with the synthesis of a higher-mol.-wt. LOS, enhanced virulence, and increased resistance to serum killing involving the classical complement pathway.

L3 ANSWER 24 OF 28 CAPLUS COPYRIGHT 1999 ACS

AN 1985:404697 CAPLUS

DN 103:4697

TI Composition and antigenic activity of the oligosaccharide moiety of **Haemophilus influenzae** type b lipooligosaccharide

SO Infect. Immun. (1985), 48(2), 324-30

CODEN: INFIBR; ISSN: 0019-9567

AU Inzana, Thomas J.; Seifert, William E., Jr.; Williams, Robert P.

PY 1985

AB The oligosaccharide moiety of the lipooligosaccharide of **H. influenzae** type b strain Eag was isolated from the lipid component by mild acid hydrolysis and purified by gel filtration. Fast atom bombardment-mass spectrometry indicated that the lipid-free oligosaccharide had a basic mol. wt. of 1768; polysaccharides comparable to high-mol.-wt. O side chains were not found. Glucose, galactose, galactosamine, heptose, 3-deoxy-D-manno-2-octulosonic acid (KDO), ethanolamine, and

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phosphate were identified in the lipid-free oligosaccharide by colorimetric assays, gas chromatog.-mass spectrometry, or amino acid anal. The presence of KDO was not clearly established by a thiobarbituric acid assay or by growth inhibition by a diazaborine deriv. thought to block KDO synthesis. However, the semicarbazide assay and gas chromatog.-mass spectrometry confirmed the presence of KDO. Lectin pptn. by Eag lipooligosaccharide in gels indicated that .beta.-D-galactose was present and that some of this monosaccharide was a terminal, nonreducing residue linked to N-acetyl-D-galactosamine. The lipid-free oligosaccharide was antigenic and completely inhibited lipooligosaccharide antibody (predominantly IgG and IgM) in an enzyme-linked immunosorbent assay, whereas the solubilized lipid A moiety did not. **H. influenzae** Type b lipid-free oligosaccharide differed from core oligosaccharide of Salmonella lipooligosaccharide by the presence of galactosamine and a smaller percentage of heptose and KDO.

L3 ANSWER 25 OF 28 CAPLUS COPYRIGHT 1999 ACS

AN 1985:94049 CAPLUS

DN 102:94049

TI A minor high-molecular-weight outer membrane protein of *Haemophilus influenzae* type b is a protective antigen

SO Infect. Immun. (1985), 47(1), 253-9

CODEN: INFIBR; ISSN: 0019-9567

AU Kimura, Alan; Gulig, Paul A.; McCracken, George H., Jr.; Loftus, Theresa A.; Hansen, Eric J.

PY 1985

AB Cell surface-exposed antigenic determinants of several high-mol.-wt. outer membrane proteins of *H. influenzae* type b (Hib) have been shown to be consistently immunogenic in human infants convalescing from Hib meningitis. A monoclonal antibody (mab), 6G12, directed against one of these cell surface-exposed outer membrane proteins that has an apparent mol. wt. of 98,000 (98K) was identified by radioimmunopptn. anal. Of 120 clin. isolates of Hib, 83 were found to possess antigenic determinants which reacted with mab 6G12 in a colony blot-radioimmunoassay procedure, indicating that the antigenic determinant recognized by mab 6G12 is present in the majority of Hib strains. A different radioimmunoassay, which uses whole Hib cells as antigen, confirmed that strains reactive with mab 6G12 in the colony blot-radioimmunoassay procedure possessed a cell surface-exposed and antibody-accessible antigenic determinant recognized by this mab. Hib strains which did not react with mab 6G12 were found to lack a 98K protein. Passive immunization with mab 6G12 reduced the level of bacteremia that developed in infant rats challenged with the homologous Hib strain against which this mab was raised. In contrast, no protection was obsd. when the challenge strain was one which lacks the antigenic determinant

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recognized by mab 6G12. Radioimmunopptn. anal. of sera from human infants convalescing from Hib meningitis detected an antibody response directed against the 98K protein. The protection against exptl. Hib disease provided by antibody to the 98K protein, the immunogenicity of this protein in human infants, and its presence in a majority of Hib strains indicate that the 98K outer membrane protein may have potential for vaccine development.

L3 ANSWER 26 OF 28 CAPLUS COPYRIGHT 1999 ACS

AN 1983:140177 CAPLUS

DN 98:140177

TI Structural studies of the *Haemophilus influenzae* capsular polysaccharides

SO *Haemophilus Influenzae*: Epidemiol., Immunol., Prev. Dis., [Pap. Conf.] (1982), Meeting Date 1981, 185-96. Editor(s): Sell, Sarah Hamilton; Wright, Peter F. Publisher: Elsevier, New York, N. Y. CODEN: 49GIAZ

AU Egan, William M.; Tsui, Fai Po; Zon, Gerald

PY 1982

AB The structures of the repeating units of the 6 H. *influenzae* serotype capsular polysaccharides (a-f) were detd. by a combination of chem. and NMR spectroscopic techniques. Four of the capsular polysaccharides were phosphate esters. All 6 polysaccharides were high-mol.-wt. polymers composed of acidic disaccharide repeat units; types a, b, c, and f were acidic as a result of phosphoric diester groups, and types d and e were acidic as a result of carboxylic acid groups. Types d and e contained the unusual capsular constituent, 2-acetamido-2-deoxy-D-mannose uronic acid.

L3 ANSWER 27 OF 28 CAPLUS COPYRIGHT 1999 ACS

AN 1978:421972 CAPLUS

DN 89:21972

TI Purification of specific precipitinogen and extraction of endotoxin from *Haemophilus influenzae*

SO J. Clin. Pathol. (1978), 31(4), 370-7

CODEN: JCPAAK; ISSN: 0021-9746

AU Van der Zwan, J. C.; Dankert, J.; De Vries, K.; Orie, N. G. M.; Kauffman, H. F.

PY 1978

AB After purifying a H. *influenzae* precipitinogen from endotoxic activity by means of ultracentrifugation, column chromatog. (Sephadex 6B), and ion exchange chromatog. (DEAE Sephadex A25) a fraction was obtained which still contained a specific precipitinogen that was virtually free of endotoxin. Furthermore, during the chromatog. procedures fractions with a high and a low mol. wt. endotoxic activity were found. The limulus lysate test was more sensitive in the high mol. wt. fractions and the LD50 in mice in the low mol. wt. fractions with

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endotoxic activity.

L3 ANSWER 28 OF 28 CAPLUS COPYRIGHT 1999 ACS  
AN 1978:168285 CAPLUS  
DN 88:168285  
TI Immunogenicity in weanling rabbits of a polyribophosphate complex  
from *Haemophilus influenzae* type b  
SO J. Infect. Dis. (1977), 136(Suppl.), 63-70  
CODEN: JIDIAQ; ISSN: 0022-1899  
AU Anderson, Porter; Smith, David H.  
PY 1977  
- AB Polyribophosphate (PRP), the capsular polysaccharide of *H. influenzae* type b, is more effectively immunogenic when it is associated with the bacterium than when it is in the purified form that is being tested as a vaccine for humans. To analyze this difference, there was isolated from *H. influenzae* type b a high-mol.-wt., sol. complex, in which PRP appears to be combined with protein (.apprx.7% protein). The pyrogenicity and limulus lysate gelation activity of the complex suggest that a small amt. of lipopolysaccharide also is present. The protein was resolved into 5 polypeptides by electrophoresis in polyacrylamide gel contg. Na dodecyl sulfate. In weanling rabbits, which do not respond to purified PRP, the complex induces high titers of antibody to PRP, in an anamnestic pattern. Bactericidal antibody to other bacterial components was also elicited. Equil. d. gradient centrifugation of the complex indicated that most of the immunogenicity of PRP resides in the least dense fractions, which are high in protein, low in polysaccharide, and active in the limulus lysate test; denser fractions that react strongly with limulus lysate but are poor in protein were much less immunogenic.

FILE 'CAPLUS' ENTERED AT 12:34:40 ON 25 MAR 1999

L4 55 SEA ABB=ON PLU=ON L1 AND ((HMW# OR HMP#) (S) MOLECUL? OR HIGH(1W) (WEIGHT OR WT))  
L5 28 SEA ABB=ON PLU=ON L4 AND (ANTIGEN OR ADHESIN OR HNI47 OR HNI 47 OR HSP OR HEAT(W) SHOCK)  
L6 0 SEA ABB=ON PLU=ON L5 NOT L3

(FILE 'MEDLINE, BIOSIS, EMBASE, LIFESCI, BIOTECHDS, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, PROMT, TOXLIT, TOXLINE, DRUGU, DRUGNL, DRUGB, DRUGLAUNCH' ENTERED AT 12:36:14 ON 25 MAR 1999)

L7 126 S L5  
L8 58 DUP REM L7 (68 DUPLICATES REMOVED)

L8 ANSWER 1 OF 58 MEDLINE  
AN 1999081722 MEDLINE

DUPLICATE 1

DN 99081722  
TI Characterization of emb, a gene encoding the major adhesin of *Streptococcus defectivus*.

Searcher : Shears 308-4994

09/210995

AU Manganelli R; van de Rijn I  
CS Department of Microbiology and Immunology, Wake Forest University  
School of Medicine, Winston-Salem, North Carolina, USA.  
NC AI37320 (NIAID)  
CA12107 (NCI)  
SO INFECTION AND IMMUNITY, (1999 Jan) 67 (1) 50-6.  
Journal code: GO7. ISSN: 0019-9567.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
OS GENBANK-AF067776  
EM 199903  
EW 19990305  
AB Streptococcus defectivus is one of the nutritionally variant streptococci, a class of viridans group streptococci first isolated from patients with endocarditis and otitis media . In previous studies, NVS-47, a clinical isolate of S. defectivus, was shown to bind to the extracellular matrix. A high -molecular-weight surface protein was identified and proposed to be responsible for mediating this binding. In the present study, the gene encoding this protein was identified by transposon mutagenesis and characterized. The gene (emb) was found to be larger than 14 kb and was partially sequenced. It encodes a protein containing at least 50 repeats of 77 amino acids predicted to assume an alternating coiled-coil conformation. The domain responsible for extracellular matrix binding was mapped to the N terminus of the protein. From sequence analysis, Emb is proposed to be the prototype of a new family of streptococcal fibrillar proteins.

L8 ANSWER 2 OF 58 MEDLINE DUPLICATE 2  
AN 1998234022 MEDLINE  
DN 98234022

TI Nasopharyngeal colonization with nontypeable Haemophilus influenzae in chinchillas.

AU Yang Y P; Loosmore S M; Underdown B J; Klein M H  
CS Research Center, Pasteur Merieux Connaught Canada, North York, Ontario.. ypyang@ca.pmc-vacc.com

SO INFECTION AND IMMUNITY, (1998 May) 66 (5) 1973-80.  
Journal code: GO7. ISSN: 0019-9567.

CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199807  
EW 19980703

AB Colonization of the nasopharynx by a middle ear pathogen is the first step in the development of otitis media in

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humans. The establishment of an animal model of nasopharyngeal colonization would therefore be of great utility in assessing the potential protective ability of candidate vaccine antigens (especially adhesins) against otitis media. A chinchilla nasopharyngeal colonization model for nontypeable *Haemophilus influenzae* (NTHI) was developed with antibiotic-resistant strains. This model does not require coinfection with a virus. There was no significant difference in the efficiency of NTHI colonization between adult (1- to 2-year-old) and young (2- to 3-month-old) animals. However, the incidence of middle ear infection following nasopharyngeal colonization was significantly higher in young animals (83 to 89%) than in adult chinchillas (10 to 30%). Chinchillas that had recovered either from a previous middle ear infection caused by NTHI or from an infection by intranasal inoculation with NTHI were completely protected against nasopharyngeal colonization with a homologous strain and were found to be the best positive controls in protection studies. Systemic immunization of chinchillas with inactivated whole-cell preparations significantly protected animals not only against homologous NTHI colonization but also partially against heterologous NTHI infection. In all protected animals, significant serum anti-P6 and anti-HMW antibody responses were observed. The outer membrane P6 and high-molecular-weight (HMW) proteins appear to be promising candidate vaccine antigens to prevent nasopharyngeal colonization and middle ear infection caused by NTHI.

L8 ANSWER 3 OF 58 MEDLINE  
 AN 1998234010 MEDLINE  
 DN 98234010  
 TI Synthesis and characterization of lipooligosaccharide-based conjugates as vaccine candidates for *Moraxella* (*Branhamella*) *catarrhalis*.  
 AU Gu X X; Chen J; Barenkamp S J; Robbins J B; Tsai C M; Lim D J; Battey J  
 CS Laboratory of Immunology, National Institute on Deafness and Other Communication Disorders, Rockville, Maryland 20850, USA..  
 SO INFECTION AND IMMUNITY, (1998 May) 66 (5) 1891-7.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; Cancer Journals  
 EM 199807  
 EW 19980703  
 AB *Moraxella* (*Branhamella*) *catarrhalis* is an important cause of  
 Searcher : Shears 308-4994



otitis media and sinusitis in children and of lower respiratory tract infections in adults. Lipooligosaccharide (LOS) is a major surface antigen of the bacterium and elicits bactericidal antibodies. Treatment of the LOS from strain ATCC 25238 with anhydrous hydrazine reduced its toxicity 20,000-fold, as assayed in the Limulus amebocyte lysate (LAL) test. The detoxified LOS (dLOS) was coupled to tetanus toxoid (TT) or high-molecular-weight proteins (HMP) from nontypeable *Haemophilus influenzae* through a linker of adipic acid dihydrazide to form dLOS-TT or dLOS-HMP. The molar ratios of dLOS to TT and HMP conjugates were 19:1 and 31:1, respectively. The antigenicity of the two conjugates was similar to that of the LOS, as determined by double immunodiffusion. Subcutaneous or intramuscular injection of both conjugates elicited a 50- to 100-fold rise in the geometric mean of immunoglobulin G (IgG) to the homologous LOS in mice after three injections and a 350- to 700-fold rise of anti-LOS IgG in rabbits after two injections. The immunogenicity of the conjugate was enhanced by formulation with monophosphoryl lipid A plus trehalose dimycolate. In rabbits, conjugate-induced antisera had complement-mediated bactericidal activity against the homologous strain and heterologous strains of *M. catarrhalis*. These results indicate that a detoxified LOS-protein conjugate is a candidate for immunization against *M. catarrhalis* diseases.

L8 ANSWER 4 OF 58 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 4  
 AN 1999:111775 BIOSIS  
 DN PREV199900111775  
 TI A putative adhesin gene cloned from *Campylobacter jejuni*.  
 AU Kelle, K.; Pages, J.-M.; Bolla, J.-M. (1)  
 CS (1) CJF 96-06, EA 2197, Faculte Med. Timone, 27 boulevard Jean  
 Moulin, 13385 Marseille Cedex 05 France  
 SO Research in Microbiology, (Nov.-Dec., 1998) Vol. 149, No. 10, pp.  
 723-733.  
 ISSN: 0923-2508.  
 DT Article  
 LA English  
 SL English; French  
 AB Thirteen *Campylobacter jejuni* strains of human origin showed differing behaviours when analysed for their ability to bind the Caco-2 cell line in vitro, suggesting variations in genetic complements and/or regulation. We designed an oligonucleotide probe corresponding to a highly conserved part of adhesins from various Gram-negative bacteria. Among our laboratory collection, Southern hybridization has demonstrated that only a discrete number of strains harbour this sequence. The corresponding gene has been cloned from our prototype strain and sequence analysis has confirmed homology with Gram-negative bacterial adhesins. The ORF

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corresponded to 869 amino acids; we named this protein P95. Protein sequence similarity assessment demonstrated that this gene product belongs to the family of proteins including the filamentous haemagglutinin of *Bordetella pertussis* and the high-molecular-weight surface-exposed adhesins of *Haemophilus influenzae*. Comparison of adhesion and hybridization results emphasized the involvement of this gene in an essential pathogenic process of *Campylobacter*.

DUPLICATE 5

L8 ANSWER 5 OF 58 MEDLINE  
 AN 1998084498 MEDLINE  
 DN 98084498  
 TI Prevalence and distribution of the hmw and hia genes-and the HMW and Hia adhesins among genetically diverse strains of nontypeable *Haemophilus influenzae*.  
 AU St. Geme J W 3rd; Kumar V V; Cutter D; Barenkamp S J  
 CS Edward Mallinckrodt Department of Pediatrics, Washington University School of Medicine, and St. Louis Children's Hospital, Missouri 63110, USA.. stgeme@borcim.wustl.edu  
 NC 1R01 DC-02873-01 (NIDCD)  
 SO INFECTION AND IMMUNITY, (1998 Jan) 66 (1) 364-8.  
 Journal code: GO7. ISSN: 0019-9567.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; Cancer Journals  
 EM 199803  
 AB Nontypeable *Haemophilus influenzae* is a common cause of human disease and initiates infection by colonizing the upper respiratory tract. In previous work we identified high-molecular-weight adhesins referred to as HMW1 and HMW2, expressed by nontypeable strain 12, and determined that most strains of nontypeable *H. influenzae* express one or two antigenically related proteins. More recently, we determined that some strains lack HMW1- and HMW2-like proteins and instead express an adhesin called Hia. In the present study, we determined the prevalence and distribution of the hmw and hia genes in a collection of 59 nontypeable strains previously characterized in terms of genetic relatedness. Based on Southern analysis, 47 strains contained sequences homologous to the hmw1 and hmw2 genes and nine strains contained homologs to hia. No strain harbored both hmw and hia, and three strains harbored neither. Although the hmw and hia genes failed to define distinct genetic divisions, the hmw-deficient strains formed small clusters or lineages within the larger population structure. Additional analysis established that the IS1016 insertion element was uniformly absent from strains containing hmw sequences but was present in two-thirds of

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09/210995

the **hmw**-deficient strains. As IS1016 is associated with the capsule locus (**cap**) in most encapsulated strains of **H. influenzae**, we speculate that **hmw**-deficient nontypeable strains evolved more recently from an encapsulated ancestor.

L8 ANSWER 6 OF 58 MEDLINE

AN 1998239408 MEDLINE

DN 98239408

TI Heterogeneity in the protein cores of mucins isolated from human middle ear effusions: evidence for expression of different mucin gene products.

AU Hutton D A; Fogg F J; Kubba H; Birchall J P; Pearson J P

CS Department of Physiological Sciences, University of Newcastle Upon Tyne, UK.

SO GLYCOCONJUGATE JOURNAL, (1998 Mar) 15 (3) 283-91.

Journal code: BJJ. ISSN: 0282-0080.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199809

EW 19980904

AB High molecular weight mucins were isolated and purified from human middle ear effusions of children with Otitis Media with Effusion (OME) classified into three groups, (1) thick and (2) thin from anatomically normal children and (3) effusions from cleft palate patients. Amino acid analyses of the purified mucins from the three pools were similar but not identical with characteristic contents of serine threonine and proline (32%, 28%, and 38% for pools (1) (2) and (3) respectively). Proteinase resistant glycopeptide fragments corresponding to the tandem repeat domains of cloned mucin genes showed marked differences both between the three mucin pools and with the composition of the tandem repeat sequences of the cloned mucin genes expressed in the airways. Studies on the antigenic identity of middle ear mucins found an epitope likely to be present on MUC5AC, but only accounting for a maximum of 15% by weight and no reactivity was found with antibodies to MUC2 or MUC1. A polyclonal antibody raised to thick effusion mucins reacted strongly with human salivary mucin suggesting the presence of MUC5B epitopes. These studies suggest that more than one mucin gene product is secreted by the human middle ear mucosa and that there may be further mucin genes expressed by the middle ear that have yet to be cloned.

L8 ANSWER 7 OF 58 SCISEARCH COPYRIGHT 1999 ISI (R)

AN 1998:98321 SCISEARCH

GA The Genuine Article (R) Number: YT330

TI Outer-membrane antigen expression by Moraxella

Searcher : Shears 308-4994

09/210995

(Branhamella) catarrhalis influences pulmonary clearance  
AU Kyd J M; Cripps A W; Murphy T F (Reprint)  
CS UNIV CANBERRA, FAC SCI APPL, BELCONNEN, ACT 2616, AUSTRALIA  
(Reprint); UNIV CANBERRA, FAC SCI APPL, BELCONNEN, ACT 2616,  
AUSTRALIA; SUNY BUFFALO, DEPT MED, DIV INFECT DIS, BUFFALO, NY  
14260; SUNY BUFFALO, DEPT MICROBIOL, BUFFALO, NY 14260  
CYA AUSTRALIA; USA  
SO JOURNAL OF MEDICAL MICROBIOLOGY, (FEB 1998) Vol. 47, No. 2, PP.  
159-168.  
Publisher: CHAPMAN HALL LTD, 2-6 BOUNDARY ROW, LONDON, ENGLAND SE1  
8HN.  
ISSN: 0022-2615.  
DT Article; Journal  
FS LIFE  
LA English  
REC Reference Count: 21  
\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*  
AB Moraxella (Branhamella) catarrhalis is a common respiratory tract  
pathogen in man. The bacterium shows a strong tendency to form  
aggregates in vitro. A variant strain of M. catarrhalis that showed  
a reduced tendency to form aggregates was selected by successive  
in-vitro passage in broth culture from which aggregates had settled.  
The non-clumping variant strain showed alteration in expression of  
outer-membrane antigens, including the HMW-OMP,  
an outer-membrane protein of c. 200 kDa, outer-membrane protein CD  
and lipo-oligosaccharide. A mouse model for pulmonary challenge with  
M. catarrhalis revealed significant differences in the rate of  
clearance of the isogenic variant strains from the lung. The parent  
strain caused enhanced recruitment of neutrophils to the lung and  
more rapid clearance of bacteria from the lungs in comparison to the  
non-clumping variant. It is concluded that alteration of expression  
of surface molecules by M. catarrhalis has a significant  
impact in an in-vivo model of pulmonary clearance.  
L8 ANSWER 8 OF 58 BIOTECHDS COPYRIGHT 1999 DERWENT INFORMATION LTD  
AN 97-13226 BIOTECHDS  
TI High mol.wt. proteins of non-typeable  
Haemophilus influenzae;  
vector expression in host cell for recombinant protein  
production and application in vaccine production  
AU Barenkamp S J  
PA Barenkamp S J  
LO Webster Grove, MO, USA.  
PI WO 9736914 9 Oct 1997  
AI WO 97-US4707 1 Apr 1997  
PRAI US 96-617697 1 Apr 1996  
DT Patent  
LA English  
OS WPI: 97-503038 [46]

Searcher : Shears 308-4994

09/210995

AN 97-13226 BIOTECHDS

AB The following are claimed: isolated and purified DNAs encoding high mol.wt. proteins HMW3 and HMW4 of a non-typeable *Haemophilus* sp., having defined DNA sequences of 4,794 and 4,803 bp and encode proteins with 1,599 and 1,600 amino acids; a vector containing the DNA for transformation of a host; an isolated and purified high mol.wt. protein retaining the immunological ability to protect against disease caused by a non-typeable *Haemophilus* sp., characterized by at least one surface-exposed B-lymphocyte epitope that is recognized by monoclonal antibody AD6; a conjugate containing the protein linked to an antigen, hapten or polysaccharide for eliciting an immune response to the antigen, hapten or polysaccharide; a synthetic peptide having a protein sequence containing 6-150 amino acids and corresponding to at least one protective epitope of the HMW1 (125 kD, 5,116 bp, 1,536 amino acids), HMW2 (120 kD, 4,937 bp, 1,477 amino acids), HMW3 (125 kD) or HMW4 (123 kD) protein, where the protein is recognized by AD6 and/or 10C5. The proteins and peptides can be used in vaccines against *Haemophilus influenzae* infection. (183pp)

L8 ANSWER 9 OF 58 SCISEARCH COPYRIGHT 1999 ISI (R)

AN 97:809230 SCISEARCH

GA The Genuine Article (R) Number: YD176

TI A protective epitope of *Moraxella catarrhalis* is encoded by two different genes

AU Aebi C; Maciver I; Latimer J L; Cope L D; Stevens M K; Thomas S E; McCracken G H; Hansen E J (Reprint)

CS UNIV TEXAS, SW MED CTR, DEPT MICROBIOL, HAMON BLDG, NA6-200, 6000 HARRY HINES BLVD, DALLAS, TX 75235 (Reprint); UNIV TEXAS, SW MED CTR, DEPT MICROBIOL, DALLAS, TX 75235; UNIV TEXAS, SW MED CTR, DEPT PEDIAT, DALLAS, TX 75235

CYA USA

SO INFECTION AND IMMUNITY, (NOV 1997) Vol. 65, No. 11, pp. 4367-4377. Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171. ISSN: 0019-9567.

DT Article; Journal

FS LIFE

LA English

REC Reference Count: 70

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB

The high-molecular-weight UspA protein of *Moraxella catarrhalis* has been described as being both present on the surface of all *M. catarrhalis* disease isolates examined to date and a target for a monoclonal antibody (MAI, 17C7) which enhanced pulmonary clearance of this organism in a mouse model system (M. E. Helminen et al., J. Infect. Dis. 170:867-872, 1994). A recombinant bacteriophage that formed plaques which bound MAb 17C7 was shown to

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contain a *M. catarrhalis* gene, designated *uspA1*, that encoded a protein with a calculated molecular weight of 88,271. Characterization of an isogenic *uspA1* mutant revealed that elimination of expression of *UspA1* did not eliminate the reactivity of *M. catarrhalis* with MAb 17C7. In addition, N-terminal amino acid analysis of internal peptides derived from native *UspA* protein and Southern blot analysis of *M. catarrhalis* chromosomal DNA suggested the existence of a second *UspA*-like protein. A combination of epitope mapping and ligation-based PCR methods identified a second *M. catarrhalis* gene, designated *uspA2*, which also encoded the MAb 17C7-reactive epitope. The *UspA2* protein had a calculated molecular weight of 62,483. Both the isogenic *uspA1* mutant and an isogenic *uspA1* mutant possessed the ability to express a very-high-molecular-weight antigen that bound MAb 17C7. Southern blot analysis indicated that disease isolates of *M. catarrhalis* likely possess both *uspA2* and *uspA2* genes. Both *UspA1* and *UspA2* most closely resembled adhesins produced by other bacterial pathogens.

L8 ANSWER 10 OF 58 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD  
 AN 98-24625 DRUGU M T  
 TI Vaccination against middle-ear bacterial and viral pathogens.  
 AU Giebink G S  
 CS Univ.Minnesota  
 LO Minneapolis, Minn., USA  
 SO Ann.N.Y.Acad.Sci. (830, 330-52, 1997) 3 Tab. 121 Ref.  
 CODEN: ANYAA9 ISSN: 0077-8923  
 AV Box 296 May, 420 Delaware Street, S.E., Minneapolis, MN 55455,  
 U.S.A. (e-mail: giebi001@maroon.tc.umn.edu).  
 LA English  
 DT Journal  
 FA AB; LA; CT  
 FS Literature  
 AN 98-24625 DRUGU M T  
 AB Vaccination against middle-ear bacterial and viral pathogens is  
 reviewed with reference to pneumococcal vaccines, conjugate  
 pneumococcal vaccines, *Haemophilus influenzae*  
 vaccines (nontypable), *Moraxella catarrhalis* vaccines, respiratory  
 viral vaccines (including influenza vaccine) and passive  
 immunoprophylaxis. *Otitis media* can be  
 prevented by systemic immunization. Passive immunoprophylaxis also  
 has potential for preventing this disease.  
 ABEX *Otitis media* can be prevented by systemic  
 immunization. Pneumococcal conjugate vaccines are being developed  
 to circumvent T-independence of these antigens and  
 provide durable immunity at a very young age. Several pneumococcal  
 conjugate vaccines are being tested clinically. Potential vaccine  
 antigens of nontypable *H. influenzae*  
 include outer membrane proteins, pili, fimbriae and high  
 Searcher : Shears 308-4994

09/210995

molecular weight proteins. Several outer membrane proteins show extensive homology among strains, but the surface determinants of others are very variable so that antibodies to surface epitopes of one strain will not bind to surface epitopes of another. Several *M. catarrhalis* outer membrane proteins and high molecular weight protein antigens have vaccine potential, but no functional correlates of protection have been identified. There is no evidence to suggest that antibodies to *M. catarrhalis* protect against otitis media. Attenuated viral vaccines may prevent childhood otitis media. 2 Clinical trials with killed influenza vaccines have shown a reduction in otitis media among vaccine recipients compared to controls during periods of high influenza disease activity in the community. Passive immunoprophylaxis may also prevent otitis media. Human bacterial polysaccharide immune globulin protects against pneumococcal otitis media in children and in a chinchilla model of otitis media. High-dose RSV-enriched Ig reduces the incidence and severity of RSV lower respiratory tract infection in high risk children. Passive immunoprophylaxis may also be effective in children with specific immune deficiencies and in patients who fail to respond to vaccines. (E83)

L8 ANSWER 11 OF 58 TOXLINE  
AN 1997:60389 TOXLINE  
DN CRISP-97-C00019-02  
TI VACCINE DEVELOPMENT OF NONTYPEABLE HAEMOPHILUS INFLUENZAE.  
AU GU X  
CS NIDCD, NIH  
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE;  
NATIONAL INST. OF HEALTH, NAT'L. INST. ON DEAFNESS & OTHER  
COMMUNICATION DISORDERS.  
NC Z01DC00019-02  
SO (1996). Crisp Data Base National Institutes Of Health. Award Type: G  
= Grant  
DT (RESEARCH)  
FS CRISP  
LA English  
EM 199705  
AB RPROJ/CRISP Nontypeable *Haemophilus influenzae* (*NTHi*) is an important cause of otitis media in children and of pneumonitis in adults with depressed resistance. There is no vaccine available for *NTHi*. Lipooligosaccharide (LOS) is a major surface antigen of *NTHi* and elicits bactericidal and opsonic antibodies. We prepared detoxified LOS (dLOS) protein conjugates from *NTHi* for use as an experimental vaccine.  
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LOS from strain 9274 was treated with anhydrous hydrazine and its toxicity was reduced to clinically acceptable levels. dLOS was bound to tetanus toxoid or high molecular weight proteins from NTHi through a linker to form conjugates. The antigenicity of the conjugates was similar to that of the LOS alone as determined by double immunodiffusion or ELISA. Subcutaneous or intramuscular injection of the conjugates elicited a 28 to 486-fold rise of IgG antibodies in mice to the homologous LOS after 2 to 3 injections, and a 169 to 243-fold rise in rabbits after 2 injections. The immunogenicity of the conjugates in mice and rabbits was enhanced by formulation with monophosphoryl lipid A plus trehalose dimycolate. In rabbits, conjugate-induced LOS antibodies induced complement-mediated bactericidal activity against the homologous strain 9274 and the heterologous strain 3189. These results indicate that a detoxified LOS-protein conjugate is a candidate vaccine for otitis media and pneumonitis caused by NTHi.

L8 ANSWER 12 OF 58 BIOTECHDS COPYRIGHT 1999 DERWENT INFORMATION LTD  
AN 96-14067 BIOTECHDS

TI Nucleic acid containing a promoter and a gene encoding a non-Bordetella gene product;

an expression system for cholera toxin or *Haemophilus influenzae* high mo.wt. outer membrane protein antigen expression in *Bordetella pertussis*

AU Loosmore S M; Yacoob R K; Zealey G R; Klein M H  
PA Connaught-Lab.

LO Willowdale, Ontario, Canada.

PI WO 9626282 29 Aug 1996

AI WO 96-CA107 23 Feb 1996

PRAI US 95-393334 23 Feb 1995

DT Patent

LA English

OS WPI: 96-425088 [42]

AN 96-14067 BIOTECHDS

AB A nucleic acid, of a specified DNA sequence, containing a promoter and a signal peptide functional in *Bordetella* and operatively coupled to a heterologous gene encoding a non-Bordetella gene product, where the gene is transcriptionally regulated by the promoter, is claimed. Also claimed are: a plasmid adapted for transformation of *Bordetella* containing the nucleic acid; and a recombinant *Bordetella* strain containing the nucleic acid optionally integrated into its genome, and which secretes the gene product. The gene product is an enzyme, antigen, immunogen, allergen, enzyme-inhibitor, hormone, lymphokine, immunoglobulin or fragment, toxin or subunit, mammalian protein, structural protein or receptor, preferably a cholera toxin B subunit. The antigen is a high mol.wt

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. outer membrane protein of a non-typable *Haemophilus influenzae* strain, preferably HMW1 or HMW2 protein. The plasmid is DS-546-1, JB-898-2-1, DS-729-1-1, DS-729-2-1, JB-1201-4, JB-1141-5, JB-1957-27, JB-1989-R-1, DS-1719-28 and DS-1732R-14, and the transformed bacterium is *B. pertussis*, *B. parapertussis*, *B. bronchiseptica* or *B. avium*, preferably *B. pertussis* 694-46 (ATCC 55,654). (61pp)

L8 ANSWER 13 OF 58 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD  
AN 97-033946 [03] WPIDS

DNC C97-010497

TI- Poly-ribosyl ribitol phosphate vaccine against diphtheria, hepatitis B etc. - stabilised by presence of aluminium based adjuvant, has increased storage stability whilst maintaining same immune response.

DC B04 D16

IN ARMINJON, F; CARTIER, J R; MARCHALL, H L; CARTIER, J

PA (INMR) PASTEUR MERIEUX SERUMS & VACCINS; (INMR) PASTEUR MERIEUX SERUMS & VACCINS SA

CYC 71

PI WO 9637222 A1 961128 (9703)\* FR 21 pp

RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA  
PT SD SE SZ UG

W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE  
HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX

NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN

FR 2734484 A1 961129 (9704) 10 pp

AU 9660086 A 961211 (9713)

NO 9705366 A 971121 (9809)

EP 828511 A1 980318 (9815) FR

R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE

SK 9701529 A3 980708 (9836)

ADT WO 9637222 A1 WO 96-FR791 960524; FR 2734484 A1 FR 95-6417 950524;  
AU 9660086 A AU 96-60086 960524; NO 9705366 A WO 96-FR791 960524, NO  
97-5366 971121; EP 828511 A1 EP 96-917554 960524, WO 96-FR791  
960524; SK 9701529 A3 WO 96-FR791 960524, SK 97-1529 960524

FDT AU 9660086 A Based on WO 9637222; EP 828511 A1 Based on WO 9637222

PRAI FR 95-6417 950524

AN 97-033946 [03] WPIDS

AB WO 9637222 A UPAB: 970129

New vaccine compsn. comprises: (a) 1 or more antigens which are high mol. wt. capsular polysaccharides of *Haemophilus influenzae* type b or poly-ribosyl-ribitol phosphate (PRP-T) coupled to the tetanus toxoid, and (b) an aluminium-based adjuvant which has a 0 point of charge of <7.2.

Also claimed is a method for the prodn. of the vaccine as above.

USE - The vaccine can be used against diphtheria, tetanus, whooping cough, hepatitis B, and poliomyelitis (claimed).

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ADVANTAGE - The vaccine has better storage stability than when the aluminium adjuvant is aluminium hydroxide, whilst maintaining the same immune response.  
Dwg.0/0

L8 ANSWER 14 OF 58 TOXLIT  
AN 1997:30168 TOXLIT  
DN CA-126-094782B  
TI Vaccine composition containing polyribosylribitol phosphate and method for making same.  
AU Arminjon F; Cartier J  
SO (1996). PCT Int. Appl. PATENT NO. 96 37222 11/28/96 (Pasteur Merieux Serums Et Vaccins S.A.).  
CY France  
DT Patent  
FS CA  
LA French  
OS CA 126:94782  
EM 199703  
AB A vaccine compn. contg. 1 or more **antigens** comprising the high mol. wt. capsular polysaccharide of the type b **Haemophilus influenza**, or polyribosylribitol phosphate, coupled to the tetanus toxoid and an aluminum-based adjuvant, wherein the aluminum-based adjuvant has, in its natural state, or following anion addn., a zero point of charge of <7.2. A method for making the vaccine compn. is also described. A vaccine compn. contained aluminum hydroxide 0.25 mg, PRP-T 10 mug, ADP and ATP 1 vaccinating dose each, phosphates 15 mumol, polio **antigen** type I, II, and III 40, 8, and 32 U resp., pertussis toxin 25 mug, buffer 0.125 mL, and water 0.5 mL.

DUPLICATE 8

L8 ANSWER 15 OF 58 MEDLINE  
AN 97047678 MEDLINE  
DN 97047678  
TI Synthesis, characterization, and immunologic properties of detoxified lipooligosaccharide from nontypeable **Haemophilus influenzae** conjugated to proteins.  
AU Gu X X; Tsai C M; Ueyama T; Barenkamp S J; Robbins J B; Lim D J  
CS Vaccine Development Unit, Laboratory of Cellular Biology, National Institute of Deafness and Other Communication Disorders, NIH, Rockville, Maryland 20850, USA.. xgu@pop.nidcd.nih.gov  
SO INFECTION AND IMMUNITY, (1996 Oct) 64 (10) 4047-53.  
Journal code: GO7. ISSN: 0019-9567.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199701  
EW 19970104

Searcher : Shears 308-4994

AB Nontypeable *Haemophilus influenzae* (NTHi) is an important cause of otitis media in children and of pneumonitis in adults with depressed resistance. Lipooligosaccharide (LOS) is a major surface antigen of NTHi and elicits bactericidal and opsonic antibodies. We prepared detoxified LOS (dLOS) protein conjugates from NTHi for use as experimental vaccines. LOS from NTHi 9274 was treated with anhydrous hydrazine and had its toxicity reduced to clinically acceptable levels. dLOS was bound to tetanus toxoid (TT) or high-molecular-weight proteins (HMPs) from NTHi through a linker of adipic acid dihydrazide to form dLOS-TT or dLOS-HMP. The molar ratio of the dLOS to protein carriers ranged from 26:1 to 50:1. The antigenicity of the conjugates was similar to that of the LOS alone as determined by double immunodiffusion. Subcutaneous or intramuscular injection of the conjugates elicited a 28- to 486-fold rise in the level of immunoglobulin G antibodies in mice to the homologous LOS after two or three injections and a 169- to 243-fold rise in the level of immunoglobulin G antibodies in rabbits after two injections. The immunogenicity of the conjugates in mice and rabbits was enhanced by formulation with monophosphoryl lipid A plus trehalose dimycolate. In rabbits, conjugate-induced LOS antibodies induced complement-mediated bactericidal activity against the homologous strain 9274 and prototype strain 3189. These results indicate that a detoxified LOS-protein conjugate is a candidate vaccine for otitis media and pneumonitis caused by NTHi.

DUPLICATE 9

L8 ANSWER 16 OF 58 MEDLINE  
 AN 96333336 MEDLINE  
 DN 96333336  
 TI Identification of surface-exposed B-cell epitopes on high molecular-weight adhesion proteins of nontypeable *Haemophilus influenzae*.  
 AU Barenkam S J; St. Geme J W 3rd  
 CS Department of Pediatrics, St. Louis University School of Medicine, Missouri, USA.  
 NC AI-21707 (NIAID)  
 DC-02873 (NIDCD)  
 SO INFECTION AND IMMUNITY, (1996 Aug) 64 (8) 3032-7.  
 Journal code: GO7. ISSN: 0019-9567.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; Cancer Journals  
 EM 199611  
 AB We previously reported that two surface-exposed high-molecular-weight proteins, HMW1 and HMW2, expressed by a prototypic strain of nontypeable

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*Haemophilus influenzae* (NTHI) mediate attachment to human epithelial cells. These proteins are members of a family of highly immunogenic proteins common to most nontypeable *Haemophilus* strains. We also reported that immunization with an HMW1-HMW2 mixture modified the course of disease in an animal model of otitis media, suggesting the potential usefulness of these proteins as NTHI vaccine components. Identification of surface-accessible B-cell epitopes could be important to efforts to develop recombinant or synthetic peptide vaccines based upon these high-molecular-weight proteins. Thus, the purpose of the present study was to identify surface-accessible epitopes on the HMW1 and HMW2 proteins by using monoclonal antibodies (MAbs) and to determine the prevalence of these epitopes among the high-molecular-weight proteins expressed by heterologous nontypeable *Haemophilus* strains. MAbs were generated by immunizing mice with high-molecular-weight proteins purified from prototype strains and were screened by immunoelectron microscopy (IEM) for the ability to recognize surface epitopes. Two MAbs, designated AD6 and 10C5, that recognized surface epitopes by IEM were recovered. In order to map the epitopes recognized by these two MAbs, we constructed a set of HMW1 and HMW2 recombinant fusion proteins using the pGEMEX vectors and examined the reactivity of the MAbs with these fusion proteins. MAb AD6 recognized an epitope in both HMW1 and HMW2 which mapped to the last 75 amino acids at the carboxy termini of the two proteins. When examined for reactivity with heterologous strains, MAb AD6 recognized high-molecular-weight proteins in 75% of 125 unrelated nontypeable *Haemophilus* strains and, in addition, reacted with three of three such strains when examined by IEM. MAb 10C5 recognized an epitope that mapped to a 155-amino-acid segment near the carboxy terminus of HMW1. This epitope was adjacent to but distinct from the AD6 epitope and was absent from HMW2. The 10C5 epitope was expressed by 40% of the AD6 reactive strains. Identification of shared surface-exposed epitopes on the high-molecular-weight adhesion proteins suggests the possibility of developing recombinant or synthetic peptide-based vaccines protective against disease caused by the majority of NTHI strains.

L8 ANSWER 17 OF 58 MEDLINE  
 AN 96238995 MEDLINE  
 DN 96238995  
 TI Evaluation of purified UspA from *Moraxella catarrhalis* as a vaccine in a murine model after active immunization.  
 AU Chen D; McMichael J C; VanDerMeid K R; Hahn D; Mininni T; Cowell J; Eldridge J  
 CS Lederle-Praxis Biologicals, West Henrietta, New York 14586-9728,  
 Searcher : Shears 308-4994

09/210995

USA.  
SO INFECTION AND IMMUNITY, (1996 Jun) 64 (6) 1900-5.  
Journal code: GO7. ISSN: 0019-9567.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199610  
AB *Moraxella catarrhalis* causes otitis media, laryngitis, and respiratory infections in humans. A high-molecular-weight outer membrane protein from this bacterium named ubiquitous surface protein A (UspA) is present on all isolates. A monoclonal antibody (MAb) to UspA that recognizes a conserved epitope of this protein has been shown to promote pulmonary clearance of bacteria in passively immunized mice. In the present study, *M. catarrhalis* heterologous isolates were screened by dot blot with a panel of four additional MAbs specific for surface-exposed epitopes of UspA from *M. catarrhalis* isolate 035E. Three of the MAbs were specific for 035E, and the fourth reacted with 17 (74%) of the 23 isolates tested. Thus, UspA contains highly conserved, semiconserved, and variable surface-exposed epitopes. The UspA was purified from the 035E isolate by ion-exchange and size-exclusion chromatography, formulated with the adjuvant QS-21, and used to immunize BALB/c mice. Upon pulmonary challenge with either 035E or the heterologous isolate TTA24, significantly fewer bacteria were recovered from the lungs of immunized mice 6 h postchallenge than from control mice. The immune sera from mice or guinea pigs contained high titers of antibodies to the homologous isolate and heterologous isolates in a whole-bacterial-cell enzyme-linked immunosorbent assay. Sera against UspA, whether prepared in mice or guinea pigs, had complement-dependent bactericidal activity toward homologous and 11 heterologous *M. catarrhalis* isolates. These results indicate that the conserved epitopes of the UspA are highly immunogenic and elicit broadly reactive and biologically functional antibodies. UspA may offer protection against *M. catarrhalis* infections and is being further evaluated as a vaccine candidate.

DUPLICATE 10

L8 ANSWER 18 OF 58 MEDLINE  
AN 96178615 MEDLINE  
DN 96178615  
TI Immunization with high-molecular-weight adhesion proteins of nontypeable *Haemophilus influenzae* modifies experimental otitis media in chinchillas.  
AU Barenkamp S J  
CS Department of Pediatrics, St. Louis University School of Medicine, Missouri, USA.  
NC AI-21707 (NIAID)

Searcher : Shears 308-4994

09/210995

SO INFECTION AND IMMUNITY, (1996 Apr) 64 (4) 1246-51.  
Journal code: GO7. ISSN: 0019-9567.

CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199607  
AB

Prevention of nontypeable *Haemophilus influenzae* otitis media by vaccination is an important health care goal. Proteins important in bacterial adherence deserve consideration as potential vaccine candidates. Two colleagues and I previously identified a family of immunogenic high-molecular-weight proteins important in adherence of nontypeable *H. influenzae* to human epithelial cells (J.W. St. Geme III, S. Falkow, and S.J. Barenkamp, Proc. Natl. Acad. Sci. USA, 90:2875-2879, 1993). In the work described here, I determined whether immunization with two such adherence proteins, HMW1 and HMW2, purified from prototype nontypeable *Haemophilus* strain 12, would modify the course of experimental otitis media caused by the homologous strain. Chinchillas received three monthly subcutaneous injections with 40 microgram of an HMW1/HMW2 protein mixture in Freud's adjuvant. One month after the last injection, animals were challenged by intrabullar inoculation with 300 CFU of nontypeable *H. influenzae* 12. Infection developed in five of five control animals versus 5 of 10 immunized animals ( $P = 0.08$ , Fisher exact, one-tailed). Among infected animals, bacterial counts in middle ear fluid specimens 7 days postchallenge were significantly greater in control animals than in immunized animals ( $P = 0.014$ , Mann-Whitney U test). Serum antibody titers following immunization were comparable in uninfected and infected animals. However, infection in immunized animals was uniformly associated with the appearance of bacteria downregulated in expression of the high-molecular-weight proteins, suggesting bacterial selection in response to immunologic pressure. Although protection following immunization was incomplete, these data suggest that the high-molecular-weight adhesion proteins are potentially important protective antigens which might represent one component of a multicomponent nontypeable *Haemophilus* vaccine.

DUPLICATE 11

L8 ANSWER 19 OF 58 MEDLINE

AN 96332658 MEDLINE

DN 96332658

TI Identification of a second family of high-molecular-weight adhesion proteins expressed by non-typable *Haemophilus influenzae*.

AU Barenkamp S J; St. Geme J W 3rd

CS Department of Pediatrics, St. Louis University School of Medicine,  
Searcher : Shears 308-4994

09/210995

Cardinal Glennon Children's Hospital, Missouri 63104, USA..  
barenksj@sluvca.slu.edu

NC AI-21707 (NIAID)  
SO MOLECULAR MICROBIOLOGY, (1996 Mar) 19 (6) 1215-23.  
Journal code: MOM. ISSN: 0950-382X.  
CY ENGLAND: United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
OS GENBANK-U38617  
EM 199611

AB We previously reported that two surface-exposed high-molecular-weight proteins, HMW1 and HMW2, expressed by a prototypic strain of non-typable *Haemophilus influenzae* (NTHI), mediate attachment to human epithelial cells. These proteins are members of a family of highly immunogenic proteins common to 70-75% of NTHI strains. NTHI strains that lack HMW1/HMW2-like proteins remain capable of efficient attachment to cultured human epithelial cells, suggesting the existence of additional adhesion molecules. We reasoned that characterization of high-molecular-weight immunogenic proteins from an HMW1/HMW2-deficient strain might identify additional adhesion proteins. A genomic library was prepared in lambda EMBL3 with chromosomal DNA from non-typable *Haemophilus* strain 11, a strain that lacks HMW1/HMW2-like proteins. The library was screened immunologically with convalescent serum from a child naturally infected with strain 11, and phage clones expressing high-molecular-weight recombinant proteins were identified by Western blot analysis. One clone was identified that expressed a protein with an apparent molecular mass greater than 200 kDa. Transformation of non-adherent *Escherichia coli* strain DH5 alpha with plasmids containing the genetic locus encoding this protein gave rise to *E. coli* transformants that adhered avidly to Chang conjunctival cells. Subcloning and mutagenesis studies localized the DNA conferring the adherence phenotype to a 4.8 kbp fragment, and nucleotide sequence analysis further localized the gene encoding the adhesion protein to a 3.3 kbp open reading frame predicted to encode a protein of 114 kDa. The gene was designated hia for *Haemophilus influenzae* adhesin. Southern analysis revealed an hia homologue in 13 of 15 HMW1/HMW2-deficient non-typable *H. influenzae* strains. In contrast, the hia gene was not present in any of 23 non-typable *H. influenzae* strains which expressed HMW1/HMW2-like proteins. Identification of this second family of high-molecular-weight adhesion proteins suggests the possibility of developing vaccines based upon a

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combination of HMW1/HMW2-like proteins and Hia-like proteins which would be protective against disease caused by most or all non-typable *H. influenzae*.

L8 ANSWER 20 OF 58 LIFESCI COPYRIGHT 1999 CSA

AN 97:95398 LIFESCI

TI High molecular weight surface proteins of non-typeable *Haemophilus*

CS ST. LOUIS UNIVERSITY

SO (1996) . US Patent 5549897; US Cl. 424/256.1 435/851 530/350.

DT Patent

FS A

LA English

AB High molecular weight surface proteins of non-typeable *Haemophilus influenzae* which exhibit immunogenic properties and genes encoding the same are described. Specifically, genes coding for two immunodominant high molecular weight proteins, HMW1 and HMW2, have been cloned, expressed and sequenced, while genes coding for high molecular proteins HMW3 and HMW4 have been cloned, expressed and partially sequenced.

L8 ANSWER 21 OF 58 PROMT COPYRIGHT 1999 IAC

AN 96:595094 PROMT

TI *Haemophilus influenzae*: "Synthesis, Characterization, and Immunologic Properties of Detoxified Lipooligosaccharide from Nontypeable *Haemophilus influenzae* Conjugated to Proteins."

SO Vaccine Weekly, (11 Nov 1996) pp. N/A.  
ISSN: 1074-2921.

LA English

WC 317

AB \*FULL TEXT IS AVAILABLE IN THE ALL FORMAT\*  
Gu, X.X.; Tsai, C.M.; Ueyama, T.; Barenkamp, S.J.; Robbins, J.B.; Lim, D.J. Infection and Immunity, October 1996;64(10):4047-4053.  
According to the authors' abstract of an article published in Infection and Immunity, "Nontypeable *Haemophilus influenzae* (NTHi) is an important cause of otitis media in children and of pneumonitis in adults with depressed resistance. Lipooligosaccharide (LOS) is a major surface antigen of NTHi and elicits bactericidal and opsonic antibodies. We prepared detoxified LOS (dLOS) protein conjugates from NTHi for use as experimental vaccines. LOS from NTHi 9274 was treated with anhydrous hydrazine and had its toxicity reduced to clinically acceptable levels, dLOS was bound to tetanus toxoid (TT) or high-molecular-weight proteins (  
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HMPs) from NTHi through a linker of adipic acid dihydrazide to form dLOS-TT or dLOS-HMP. The molar ratio of the dLOS to protein carriers ranged from 26:1 to 50:1. The antigenicity of the conjugates was similar to that of the LOS alone as determined by double immunodiffusion. Subcutaneous or intramuscular injection of the conjugates elicited a 28- to 486-fold rise in the level of immunoglobulin G antibodies in mice to the homologous LOS after two or three injections and a 169- to 243-fold rise in the level of immunoglobulin G antibodies in rabbits after two injections. The immunogenicity of the conjugates in mice and rabbits was enhanced by formulation with monophosphoryl lipid A plus trehalose dimycolate. In rabbits, conjugate-induced LOS antibodies induced complement-mediated bactericidal activity against the homologous strain 9274 and prototype strain 3189. These results indicate that a detoxified LOS-protein conjugate is a candidate vaccine for otitis media and pneumonitis caused by NTHi." The corresponding author for this study is: XX Gu, Nidocd, NIH, Vaccine Dev Unit, Lab Cellular Biol, 5 Res CT, RM 2A31, Rockville, MD 20850 USA. For subscription information for this journal contact the publisher: Amer Soc Microbiology, 1325 Massachusetts Avenue, NW, Washington, DC 20005-4171.  
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L8 ANSWER 22 OF 58 PROMT COPYRIGHT 1999 IAC

AN 96:590170 PROMT

TI **Haemophilus influenzae** "Synthesis, Characterization, and Immunologic Properties of Detoxified Lipooligosaccharide from Nontypeable **Haemophilus influenzae** Conjugated to Proteins."

SO Disease Weekly Plus, (11 Nov 1996) pp. N/A.

LA English

WC 317

\*FULL TEXT IS AVAILABLE IN THE ALL FORMAT\*

AB Gu, X.X.; Tsai, C.M.; Ueyama, T.; Barenkamp, S.J.; Robbins, J.B.; Lim, D.J.

Infection and Immunity, October 1996;64(10):4047-4053.

According to the authors' abstract of an article published in Infection and Immunity, "Nontypeable **Haemophilus influenzae** (NTHi) is an important cause of

otitis media in children and of pneumonitis in adults with depressed resistance. Lipooligosaccharide (LOS) is a

major surface antigen of NTHi and elicits bactericidal and opsonic antibodies. We prepared detoxified LOS (dLOS) protein conjugates from NTHi for use as

experimental vaccines. LOS from NTHi 9274 was treated with anhydrous hydrazine and had its toxicity reduced to clinically acceptable levels, dLOS was bound to tetanus toxoid (TT) or high-molecular-weight proteins (

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09/210995

HMPs) from NTHi through a linker of adipic acid dihydrazide to form dLOS-TT or dLOS-HMP. The molar ratio of the dLOS to protein carriers ranged from 26:1 to 50:1. The antigenicity of the conjugates was similar to that of the LOS alone as determined by double immunodiffusion. Subcutaneous or intramuscular injection of the conjugates elicited a 28- to 486-fold rise in the level of immunoglobulin G antibodies in mice to the homologous LOS after two or three injections and a 169- to 243-fold rise in the level of immunoglobulin G antibodies in rabbits after two injections. The immunogenicity of the conjugates in mice and rabbits was enhanced by formulation with monophosphoryl lipid A plus trehalose dimycolate. In rabbits, conjugate-induced LOS antibodies induced complement-mediated bactericidal activity against the homologous strain 9274 and prototype strain 3189. These results indicate that a detoxified LOS-protein conjugate is a candidate vaccine for otitis media and pneumonitis caused by NTHi." The corresponding author for this study is: XX Gu, Nidocd, NIH, Vaccine Dev Unit, Lab Cellular Biol, 5 Res CT, RM 2A31, Rockville, MD 20850 USA. For subscription information for this journal contact the publisher: Amer Soc Microbiology, 1325 Massachusetts Avenue, NW, Washington, DC 20005-4171.

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DUPLICATE 12

L8 ANSWER 23 OF 58 MEDLINE  
AN 95310001 MEDLINE

DN 95310001

TI Binding of *Haemophilus influenzae* to purified  
mucins from the human respiratory tract.

AU Davies J; Carlstedt I; Nilsson A K; Hakansson A; Sabharwal H; van  
Alphen L; van Ham M; Svanborg C

CS Department of Medical and Physiological Chemistry, Lund University,  
Sweden..

SO INFECTION AND IMMUNITY, (1995 Jul) 63 (7) 2485-92.  
Journal code: G07. ISSN: 0019-9567.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199509

AB Mucins are high-molecular-weight glycoproteins  
and major constituents of the mucus layer which covers the airway  
surface. We have studied the interactions between bacteria, mucins,  
and epithelial cells from the human respiratory tract. Nontypeable  
strains of *Haemophilus influenzae* were found to  
bind to purified airway mucins in suspension and on solid phase.  
Mucins in suspension inhibited the attachment of these strains to  
nasopharyngeal epithelial cells, while mucin coating of the cells  
enhanced their binding. In contrast, strains of *Streptococcus*  
*pneumoniae* and encapsulated and other nontypeable H.

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09/210995

*influenzae* strains failed to interact with mucins. These *H. influenzae* strains used other strategies for adherence to epithelial cells. The type b strain 770235 attached via fimbriae but also expressed a subcapsular adhesin that was detected in a capsule- and fimbria-defective mutant. Mucin pretreatment of these bacteria did not inhibit adherence, but mucin pretreatment of epithelial cells inhibited adherence, probably by shielding of the receptors for these adhesins. Non-mucin-binding nontypeable and encapsulated *H. influenzae* strains would, therefore, adhere only after disruption of the mucus layer and exposure of cellular receptors. Differences in tissue toxicity and invasiveness among *H. influenzae* strains may also be influenced by the mucin interactions of the strains.

L8 ANSWER 24 OF 58 SCISEARCH COPYRIGHT 1999 ISI (R)  
AN 95:60968 SCISEARCH  
GA The Genuine Article (R) Number: QA649  
TI HUMAN IMMUNE-RESPONSE AGAINST OUTER-MEMBRANE PROTEINS OF MORAXELLA  
(BRANHAMELLA) CATARRHALIS DETERMINED BY IMMUNOBLOTTING AND  
AU ENZYME-IMMUNOASSAY  
HELMINEN M E; BEACH R; MACIVER I; JAROSIK G; HANSEN E J; LEINONEN M  
(Reprint)  
CS NATL PUBL HLTH INST, DEPT OULU, POB 310, SF-90101 OULU, FINLAND  
(Reprint); NATL PUBL HLTH INST, DEPT OULU, SF-90101 OULU, FINLAND;  
NATL PUBL HLTH INST, SF-00300 HELSINKI, FINLAND; UNIV TEXAS, SW MED  
CTR, DEPT MICROBIOL, DALLAS, TX, 75235  
CYA FINLAND; USA  
SO CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, (JAN 1995) Vol. 2,  
No. 1, pp. 35-39.  
ISSN: 1071-412X.  
DT Article; Journal  
FS CLIN  
LA ENGLISH  
REC Reference Count: 42  
\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*  
AB The role of *Moraxella* (*Branhamella*) *catarrhalis* as a respiratory  
tract pathogen is increasingly recognized. We looked at the human  
immune response against individual outer membrane proteins of *M.*  
*catarrhalis* and against the 81-kDa CopB protein, which has  
previously been shown to be a target for protective antibodies.  
Paired serum samples from six elderly patients with pneumonia were  
tested by Western blot (immunoblot) analysis by using outer membrane  
vesicles of *M. catarrhalis* 035E as antigen. All of the six  
convalescent-phase serum samples reacted with a protein which  
migrated at the position of the CopB protein and with a high  
-molecular-weight protein of *M. catarrhalis*; three serum  
samples also reacted with a 34-kDa outer membrane protein. Paired  
serum samples from 18 patients, 10 of which had *M. catarrhalis*  
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infection on the basis of previous serology results, were tested by enzyme immunoassay (EIA) with the CopB protein and whole cells of *M. catarrhalis* 035E as antigens. Nine patients showed a significant rise in EIA titer between acute- and convalescent-phase sera when whole bacterial cells were used as antigens. Six (67%) patient samples that were positive by the EIA with the whole-cell antigen were also positive by the EIA with the CopB antigen, and six of nine patient samples negative by the EIA with the whole-cell antigen were also negative by the EIA with the CopB antigen. These results suggest that both the CopB and a high-molecular-weight protein are major targets of the immune response against *M. catarrhalis*, and further studies with greater amounts of patient materials are needed to elucidate the usefulness of CopB as an antigen in etiologic studies.

L8 ANSWER 25 OF 58 BIOTECHDS COPYRIGHT 1999 DERWENT INFORMATION LTD  
AN 94-15222 BIOTECHDS  
TI New immunogenic high molecular weight proteins  
of non-typeable *Haemophilus*;  
*Haemophilus influenza* recombinant protein  
HMW1, HMW2, HMW3 and HMW4 production for use as a native or  
recombinant vaccine against sinusitis, bronchitis,  
otitis media, etc.

PA Barenkamp S J

PI WO 9421290 29 Sep 1994

AI WO 94-US2550 15 Mar 1994

PRAI US 93-38682 16 Mar 1993

DT Patent

LA English

OS WPI: 94-316665 [39]

AN 94-15222 BIOTECHDS

AB A vaccine against disease caused by non-typeable (nt)

*Haemophilus influenzae*, including otitis

media, sinusitis and bronchitis, comprises an effective  
amount of a high mol.wt. protein (I) of nt

*H. influenzae*, especially HMW1, HMW2, HMW3 or

HMW4, or their immunologically active variants or fragments or  
synthetic peptides, and a physiological adjuvant. The DNA

sequences of the gene encoding the *H. influenza*

HMW1 and HM2 and the partial sequences of HMW3 and HMW4 proteins

are disclosed (4,116, 4,937, 4,287 and 4,702 bp, respectively)  
together with derived protein sequences. (I) are useful in

vaccines against diseases not controlled by *H.*

*influenza* type b vaccines. (I) are present on most nt

*Haemophilus* spp. so should be useful in a universal *Haemophilus*

vaccine. Apart from use as vaccine antigens, (I) can be

used in conjugate vaccines with protective *H.*

*influenza* type b polysaccharides against meningitis. Nt

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Haemophilus strain 12 was digested with SauIIIA and ligated into phage lambda. Phage lambda was grown in Escherichia coli LE392 and clones recognized by serum containing a high antibody titer against (I) were isolated. (127pp)

L8 ANSWER 26 OF 58 BIOSIS COPYRIGHT 1999 BIOSIS  
AN 1995:790 BIOSIS  
DN PREV199598015090  
TI Early events in the pathogenesis of *Haemophilus*

*influenzae* disease.

AU St Geme, Joseph W. Iii

CS Dep. Mol. Microbiol., Washington Univ. Sch. Med., 660 S. Euclid Ave., Box 8230, St. Louis, MO 63110 USA

SO Miller, V. L. [Editor]; Kaper, J. B. [Editor]; Portnoy, D. A. [Editor]; Isberg, R. R. [Editor]. (1994) pp. 157-172. Molecular genetics of bacterial pathogenesis: A tribute to Stanley Falkow. Publisher: American Society for Microbiology (ASM) Books Division, 1325 Massachusetts Ave. NW, Washington, DC 20005-4171, USA. ISBN: 1-55581-082-9.

DT Book; General Review

LA English

DUPLICATE 14

L8 ANSWER 27 OF 58 MEDLINE

AN 95012637 MEDLINE

DN 95012637

TI Localization of high-molecular-weight adhesion proteins of nontypeable *Haemophilus influenzae* by immunoelectron microscopy.

AU Bakaletz L O; Barenkamp S J

CS Department of Otolaryngology, Ohio State University College of Medicine, Columbus..

NC AI 21707 (NIAID)

SO INFECTION AND IMMUNITY, (1994 Oct) 62 (10) 4460-8.

Journal code: GO7. ISSN: 0019-9567.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199501

AB A family of high-molecular-weight (HMW) surface-exposed proteins important in the attachment of nontypeable *Haemophilus influenzae* (NTHi) to human epithelial cells was previously identified (J. W. St. Geme III, S. Falkow, and S. J. Barenkamp, Proc. Natl. Acad. Sci. USA 90:2875-2879, 1993). In the present investigation, indirect immunogold labeling and electron microscopy were used to localize these proteins on three clinical isolates of NTHi, mutants deficient in expression of one or both HMW proteins, and embedded sections of human oropharyngeal cells after incubation with

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NTHi strain 12. The filamentous material comprising the proteins was labeled with monoclonal antibodies directed against two prototype HMW proteins (HMW1 and HMW2) of prototype NTHi strain 12. Gold labeling was observed as a cap or discrete aggregate off one pole or centrally along one long axis of the bacterial cell. Heavily labeled, non-bacterial-cell-associated, disk-like aggregates of the HMW proteins were frequently noted in both bacterial preparations as well as in association with the oropharyngeal cell surface and intracellularly. Mutants demonstrated diminished labeling or an absence thereof, respectively, which correlated well with their previously demonstrated reduced ability or inability to adhere to Chang conjunctival epithelial cells in vitro. The Haemophilus HMW proteins share antigenic determinants with and demonstrate amino acid sequence similarity to the filamentous hemagglutinin protein of Bordetella pertussis, a critical adhesin of that organism. The studies presented here demonstrate that the Haemophilus proteins and B. pertussis filamentous hemagglutinin show impressive morphologic and perhaps additional functional similarity.

L8 ANSWER 28 OF 58 LIFESCI COPYRIGHT 1999 CSA  
AN 95:7493 LIFESCI

TI High-molecular-weight proteins of nontypeable  
Haemophilus influenzae mediate bacterial adhesion  
to cellular proteoglycans

AU Noel, G.J.; Love, D.C.; Mosser, D.M.  
CS Dep. Pediatr., Div. Pediatr. Infect. Dis. and Immunol., Cornell  
Univ. Med. Coll., New York, NY 10021, USA

SO INFECT. IMMUN., (1994) vol. 62, no. 9, pp. 4028-4033.  
ISSN: 0019-9567.

DT Journal

FS J

LA English

SL English

AB A family of high-molecular-weight (  
HMW) surface-exposed proteins of nontypeable

Haemophilus influenzae (NT H.  
influenzae) mediated adherence of these organisms to human  
epithelium. To better understand the molecular basis for  
this adherence, the role of glycosaminoglycans (GAGs), substances  
commonly expressed on cell surfaces, was examined. Bacterial  
adherence to cells with specific deficiencies in GAG biosynthesis  
was measured. HMW protein-dependent bacterial adherence to  
normal cells was significantly greater than adherence to cells  
deficient in sulfated GAGs or to cells deficient in heparan sulfate  
but overexpressing chondroitin sulfate. Cells expressing  
undersulfated heparan sulfate exhibited intermediate levels of  
bacterial adherence. The addition of exogenous dextran sulfate or  
heparin inhibited over 70% of the adherence of NT H.

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*influenzae* to normal cells, whereas hyaluronic acid and chondroitin sulfate tested at the same concentration (100  $\mu$ g/ml) inhibited bacterial adherence by less than 11%. Treatment of cells with heparinase significantly reduced bacterial adherence. Following electrophoretic separation, HMW proteins were shown to bind directly to radiolabeled heparin. These results indicate that HMW protein-dependent adherence of NT H. *influenzae* is mediated by cellular sulfated GAGs and that heparan sulfate may be the predominant GAG involved in this process. However, the decreased adherence of bacteria to cells expressing undersulfated heparan sulfate and the inhibition of bacterial adherence by the addition of exogenous dextran sulfate suggest that bacterial adhesion to mammalian cells is likely to be influenced by a variety of factors, including the degree of sulfation and the specificity of the carbohydrate moieties contained in the cellular proteoglycans.

DUPLICATE 15

L8 ANSWER 29 OF 58 MEDLINE  
AN 94341895 MEDLINE  
DN 94341895  
TI The HMW1 adhesin of nontypeable *Haemophilus*

*influenzae* recognizes sialylated glycoprotein receptors on cultured human epithelial cells.

AU St. Geme J W 3rd  
CS Edward Mallinckrodt Department of Pediatrics, Washington University  
School of Medicine, St. Louis, Missouri 63110.  
NC HD-29678 (NICHD)  
SO INFECTION AND IMMUNITY, (1994 Sep) 62 (9) 3881-9.  
Journal code: GO7. ISSN: 0019-9567.

CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199411

AB Disease due to nontypeable *Haemophilus influenzae* begins with colonization of the upper respiratory tract mucosa. We recently reported that two surface-exposed high-molecular-weight proteins (HMW1 and HMW2) expressed by a prototypic strain of nontypeable H. *influenzae* mediate attachment to cultured epithelial cells. In the present study, we examined the nature of the epithelial cell receptor with which HMW1 interacts. Both proteinase K pretreatment and periodate oxidation of epithelial monolayers resulted in a marked decrease in HMW1-mediated binding, suggesting interaction with a glycoprotein structure. Treatment with peptide-N-glycosidase F produced a similar decrease in attachment and thereby provided further evidence for this conclusion. Desialylation of the epithelial cell surface also reduced binding, implying the presence of sialic acid in the

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receptor structure. Furthermore, lectins specific for terminal alpha 2-3-linked sialic acid were capable of inhibiting HMW1-mediated attachment. In summary, our results indicate that the HMW1 adhesin interacts with a glycoprotein receptor containing N-linked oligosaccharide chains with sialic acid in an alpha 2-3 configuration.

DUPLICATE 16

L8 ANSWER 30 OF 58 MEDLINE

AN 94149333 MEDLINE

DN 94149333

TI High-molecular-weight surface-exposed proteins of *Haemophilus influenzae* mediate binding to macrophages.

AU Noel G J; Barenkamp S J; St Geme J W 3rd; Haining W N; Mosser D M

CS Division of Pediatric Infectious Diseases and Immunology, Cornell University Medical College, New York, New York..

NC AI-30063 (NIAID)

SO JOURNAL OF INFECTIOUS DISEASES, (1994 Feb) 169 (2) 425-9.

Journal code: IH3. ISSN: 0022-1899.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 199405

AB The molecular basis for direct bacteria-macrophage interactions that distinguishes nontypeable (NT) *Haemophilus influenzae* from type b organisms is not known. Because of similarities between filamentous hemagglutinin (FHA) adhesin of *Bordetella pertussis* and high-molecular-weight (HMW) proteins commonly expressed by NT *H. influenzae*, the role that HMW proteins play in determining NT *H. influenzae* -macrophage interactions was assessed. In tests with genetically engineered organisms, HMW protein-expressing bacteria bound significantly better than isogenic HMW protein-deficient bacteria to macrophages. HMW protein-dependent binding to macrophages is trypsin-sensitive, is independent of divalent cations, does not occur via the leukocyte integrin CD11b/CD18, and is not affected by galactose-containing carbohydrates. Organisms bound via HMW proteins remain largely extracellular and viable. Like FHA of *Bordetella* organisms, HMW proteins mediate binding of NT *H. influenzae* to macrophages. However, unlike the interaction determined by FHA, this interaction is characteristically one of adhesion and requires additional serum opsonization for efficient killing of bacteria by macrophages.

L8 ANSWER 31 OF 58 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE

17

Searcher : Shears 308-4994



09/210995

AN 94375620 EMBASE  
DN 1994375620  
TI Adherence and invasion of *Haemophilus influenzae*

AU van Alphen L.; van Ham S.M.  
CS Department of Medical Microbiology, University of Amsterdam,  
Academic Medical Centre, Meibergdreef 15, NL-1105 AZ Amsterdam,  
Netherlands

SO Reviews in Medical Microbiology, (1994) 5/4 (245-255).  
ISSN: 0954-139X CODEN: RMEMER

CY United Kingdom

DT Journal; General Review

FS 004 Microbiology

LA English

SL English

AB Adherence of *Haemophilus influenzae* to epithelial cells plays a central role in colonization and is the first step in infection. It allows *H. influenzae* to establish itself, adapt to local conditions required for localized growth of the bacteria, and resist mechanical clearance mechanisms of the host. Bound to the cells the organism can evoke localized effects on the tissue which may lead to an inflammatory reaction, or the penetration of the bacteria between the cells into the tissues underlying the epithelium. Various adhesins, including fimbriae and high-molecular-weight outer membrane proteins, promote binding to different receptors, resulting in tissue tropism. A variety of other bacterial determinants, including the capsule and LPS, also contribute to the establishment and course of the infection. The occurrence of random and reversible fimbrial phase variation ensures the generation of a genetically and phenotypically diverse bacterial population. The diversity allows properly equipped *H. influenzae* cells (fimbriated on epithelia and non-fimbriated in the blood) to be present at random in the bacterial population, not selected for a particular fimbrial phenotype. Subsequently, natural conditions will drive selection of a particular phenotype required for survival in a specific host tissue site (mucosa, blood, etc).

L8 ANSWER 32 OF 58 BIOSIS COPYRIGHT 1999 BIOSIS

AN 1994:248909 BIOSIS

DN PREV199497261909

TI Molecular characterization of nontypable  
*Haemophilus influenzae* (NTHI) variant  
strains down-regulated in expression of high  
molecular weight (HMW) adhesion  
proteins.

AU Barenkamp, Stephen J.

CS St. Louis Univ. Sch. Med., Pediatric Res. Inst., St. Louis, MO USA

SO Pediatric Research, (1994) Vol. 35, No. 4 PART 2, pp. 173A.

Searcher : Shears 308-4994

09/210995

Meeting Info.: 104th Annual Meeting of the American Pediatric Society and the 63rd Annual Meeting of the Society for Pediatric Research Seattle, Washington, USA May 2-5, 1994  
ISSN: 0031-3998.

DT Conference  
LA English

L8 ANSWER 33 OF 58 BIOTECHDS COPYRIGHT 1999 DERWENT INFORMATION LTD  
AN 93-14467 BIOTECHDS  
TI **High molecular weight protein of non-typeable**

Haemophilus;  
recombinant HMW1, HMW2, HMW3 and HMW4 protein immunogen  
production by vector expression for use in recombinant vaccine

PA Barenkamp S J  
PI WO 9319090 30 Sep 1993  
AI WO 93-US2166 16 Mar 1993  
PRAI GB 92-5704 16 Mar 1992  
DT Patent  
LA English  
OS WPI: 93-320683 [40]  
AN 93-14467 BIOTECHDS  
AB An isolated and purified gene (I) encoding a high mol.

wt. protein (II) (preferably HMW1, HMW2, HMW3 or HMW4 or their variants or fragments) of a non-typeable Haemophilus strain (NTHS) is claimed. (II) is useful as an immunogen in native or recombinant vaccines against NTHS diseases. The DNA sequence of (I) and the protein sequences of (II) are disclosed. The following are also claimed: (1) a purified and isolated gene cluster comprising (I) encoding (II) and at least 1 downstream expression control sequence, especially (I) encoding HMW1 and HMW2 and 2 downstream control sequences; (2) HMW1 and HMW2 of mol.wt. 125,000 and 120,000, respectively, useful for NTHS disease prevention; (3) HMW1, HMW2, HMW3 or HMW4 which is antigenically related to the filamentous hemagglutinin surface protein of Bordetella pertussis; (4) a conjugate of (I) linked to a hapten, antigen or polysaccharide (protective against Haemophilus influenzae type b) for eliciting an immune response to the hapten, antigen or polysaccharide; and (5) a synthetic peptide of protein sequence (HMW1, HMW2, HMW3 or HMW4) corresponding to at least 1 protective epitope of (II) of H . influenzae. (96pp)

L8 ANSWER 34 OF 58 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD  
AN 93-320683 [40] WPIDS  
CR 94-316665 [39]  
DNC C93-142729  
TI **High molecular weight surface proteins - of**  
non-typeable haemophilus which exhibit immunogenic properties.  
DC B04 D16

Searcher : Shears 308-4994

09/210995

IN BARENKAMP, S J; ST, GEME J W  
PA (UYSL-N) UNIV ST LOUIS; (UNIW) UNIV WASHINGTON; (BARE-I) BARENKAMP S  
J; (INRM) INSERM INST NAT SANTE & RECH MEDICALE

CYC 27

PI WO 9319090 A1 930930 (9340)\* EN 96 pp  
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE  
W: AU BR CA FI JP KR NO RU UA US  
AU 9339168 A 931021 (9407)  
NO 9403431 A 941110 (9505)  
EP 632814 A1 950111 (9506) EN  
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE  
FI 9404273 A 941115 (9506)  
JP 07506248 W 950713 (9536) 29 pp  
AU 669360 B 960606 (9630)  
US 5549897 A 960827 (9640) 100 pp  
EP 632814 A4 960313 (9642)  
US 5603938 A 970218 (9713) 100 pp  
BR 9306109 A 971118 (9802)  
JP 2810235 B2 981015 (9846) 115 pp

ADT WO 9319090 A1 WO 93-US2166 930316; AU 9339168 A AU 93-39168 930316;  
NO 9403431 A WO 93-US2166 930316, NO 94-3431 940915; EP 632814 A1 EP  
93-908295 930316, WO 93-US2166 930316; FI 9404273 A WO 93-US2166  
930316, FI 94-4273 940915; JP 07506248 W JP 93-516604 930316, WO  
93-US2166 930316; AU 669360 B AU 93-39168 930316; US 5549897 A US  
93-38682 930316; EP 632814 A4 EP 93-908295 ; US 5603938 A WO  
93-US2166 930316, US 94-302832 941005; BR 9306109 A BR 93-6109  
930316, WO 93-US2166 930316; JP 2810235 B2 JP 93-516604 930316, WO  
93-US2166 930316

FDT AU 9339168 A Based on WO 9319090; EP 632814 A1 Based on WO 9319090;  
JP 07506248 W Based on WO 9319090; AU 669360 B Previous Publ. AU  
9339168, Based on WO 9319090; US 5603938 A Based on WO 9319090; BR  
9306109 A Based on WO 9319090; JP 2810235 B2 Previous Publ. JP  
07506248, Based on WO 9319090

PRAI GB 92-5704 920316

AN 93-320683 [40] WPIDS

CR 94-316665 [39]

AB WO 9319090 A UPAB: 961025

An isolated and purified gene exceeding a high mol.  
wt. (HNV) protein (I) of a non-typeable Haemophilis strain  
(HP).

Also claimed are: (A) a purified and isolated gene cluster  
comprising a nucleotide sequence (NS) for a structural gene encoding  
(I) of a non-typeable HP; and more than 1 downstream NS for on  
accessory gene for affecting expression of a gene product fully  
enclosed by the structural gene. (B) (I) of non-typeable HP encoded  
by a gene as above, or its variant or fragment retaining the  
immunological ability to protect against disease caused by a  
non-typeable HP; (C) on isolated and purified (I) of non-typeable HV  
filaments haemagglutinin surface protein of Bordetella pertussis, (D)

Searcher : Shears 308-4994

09/210995

a conjugate comprising (I) linked to an antigen, hapten or polysaccharide for eliciting an immune response to the antigen, hapten or polysaccharide; and (E) a synthetic peptide having an amino acid sequence corresponding to more than 1 protective epitope of a HMW protein of non-typeable *H. influenzae*.

ADVANTAGE - With the isolation of and purification of (I), it is possible to determine the major protective epitopes by conventional epitope mapping and synthesise peptide corresponding to these determinants to be incorporated in fully synthetic or recombinant vaccines

Dwg.0/10

Dwg.0/10

ABEQ US 5549897 A UPAB: 961007

A vaccine against disease caused by non-typeable *Haemophilus influenzae*, including otitis media, sinusitis and bronchitis, comprising an effective amount of a high molecular weight protein of non-typeable *Haemophilus influenzae* which is protein HMW1 and/or HMW2 and a physiological carrier therefor.

Dwg.0/10

ABEQ US 5603938 A UPAB: 970326

A 1536 amino acid (sequence given in the specification) high molecular weight non-typeable *Haemophilus influenzae* surface protein and a 5116 base pair DNA sequence (also given in the specification) are new.

Dwg.0/10

L8 ANSWER 35 OF 58 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD

AN 93-093726 [11] WPIDS

DNN N93-071760 DNC C93-041417

TI Antigenic proteins derived from *Moraxella catarrhalis* outer membranes - useful for diagnosing and treating *M. catarrhalis* infections.

DC B04 D16 S03

IN HANSEN, E J; HELMINEN, M; MACIVER, I

PA (TEXA) UNIV TEXAS SYSTEM; (TEXA) UNIV TEXAS; (AMCY) AMERICAN CYANAMID CO

CYC 38

PI WO 9303761 A1 930304 (9311)\* EN 73 pp

RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA SE

W: AT AU BB BG BR CA CH CS DE DK ES FI GB HU JP KP KR LK LU MG

MN MW NL NO PL RO RU SD SE US

AU 9224878 A 930316 (9328)

NO 9400502 A 940328 (9422)

FI 9400681 A 940407 (9424)

EP 612250 A1 940831 (9433) EN

R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL SE

Searcher : Shears 308-4994

JP 07501210 W 950209 (9515)  
 AU 666329 B 960208 (9613)  
 EP 612250 B1 960724 (9634) EN 29 pp  
 R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL SE  
 DE 69212495 E 960829 (9640)  
 US 5552146 A 960903 (9641) 15 pp  
 ES 2092696 T3 961201 (9704)  
 US 5599693 A 970204 (9711) 17 pp  
 US 5759813 A 980602 (9829)

ADT WO 9303761 A1 WO 92-US6869 920814; AU 9224878 A AU 92-24878 920814;  
 NO 9400502 A WO 92-US6869 920814, NO 94-502 940214; FI 9400681 A WO  
 92-US6869 920814, FI 94-681 940214; EP 612250 A1 EP 92-918273  
 920814, WO 92-US6869 920814; JP 07501210 W WO 92-US6869 920814, JP  
 93-504481 920814; AU 666329 B AU 92-24878 920814; EP 612250 B1 EP  
 92-918273 920814, WO 92-US6869 920814; DE 69212495 E DE 92-612495  
 920814, EP 92-918273 920814, WO 92-US6869 920814; US 5552146 A US  
 91-745591 910815; ES 2092696 T3 EP 92-918273 920814; US 5599693 A  
 Div ex US 91-745591 910815, US 95-450002 950525; US 5759813 A Cont  
 of US 91-745591 910815, Cont of WO 92-US6869 920814, US 94-193150  
 940919

FDT AU 9224878 A Based on WO 9303761; EP 612250 A1 Based on WO 9303761;  
 JP 07501210 W Based on WO 9303761; AU 666329 B Previous Publ. AU  
 9224878, Based on WO 9303761; EP 612250 B1 Based on WO 9303761; DE  
 69212495 E Based on EP 612250, Based on WO 9303761; ES 2092696 T3  
 Based on EP 612250; US 5759813 A Cont of US 5552146

PRAI US 91-745591 910815; US 95-450002 950525; US 94-193150 940919

AN 93-093726 [11] WPIDS

AB WO 9303761 A UPAB: 970612

Compsn. contains a purified protein or peptide **antigen**  
 (Ag) that includes an epitope immunologically cross-reactive with  
 the 30 kD, 80 kD or **high mol. wt.** (

**HMW**) outer-membrane proteins (OMP) of *Moraxella catarrhalis*.

Also new are (1) DNA segments (I) encoding Ag; (2) recombinant  
 vectors and host cells contg. (I); (3) antibodies (Ab) against Ag  
 and (4) kits for detecting Ag or Ab.

Ag is pref. one of the specified OMP, or a peptide (of 10-50  
 amino acids) contg. an appropriate epitope. Esp. it contains no  
 epitopes from other *M. catarrhalis* **antigens**.

USE - Ag and Ab are useful, in standard immunoassays, for  
 detecting the other binding partner, i.e. for diagnosis of *M.*  
*catarrhalis* infections (partic. **otitis media**).

Ab can be used to induce tolerance (passive immunisation) while Ag  
 are used as active ingredients in protective vaccines. Ab, partic.  
 those which recognise the 30 kD and HMW OMP, are reactive with a  
 wide range of pathogen subtypes and isolates. Ab can also be used  
 for purificn. of Ag. (I) can be used to express recombinant Ag, and  
 nucleic acid fragments can also be used as hybridisation probes or  
 PCR primers for detection of *M. catarrhali*

Dwg.0/5

Searcher : Shears 308-4994

09/210995

ABEQ EP 612250 B UPAB: 960829

An **antigen** composition comprising a purified protein or peptide **antigen** incorporating an epitope that is immunologically cross-reactive with *M. catarrhalis* 30 kD or HMWP OMP.

Dwg.0/5

ABEQ US 5552146 A UPAB: 961011

An **antigen** composition comprising an *Moraxella catarrhalis* outer membrane **antigen** selected from the group consisting of *M. catarrhalis* outer membrane **antigens** immunologically reactive with monoclonal antibody 10F3 (ATCC HB 11092) or 17C7 (ATCC 11093), wherein said **antigen** is purified free of other *M. catarrhalis* outer membrane **antigens**.

Dwg.0/3

ABEQ US 5599693 A UPAB: 970313

Preparing an **antigen** compsn. comprises:

(a) selecting cells expressing a *Moraxella catarrhalis* outer membrane protein or peptide **antigen** having an epitope that binds to a monoclonal antibody selected from the group consisting of 8B6 (ATCC HB 11091), 10F3 (ATCC HB 11092) and 17C7 (ATCC HB 11093);

(b) culturing the selected cells under conditions effective for expression of the **antigen**; and

(c) collecting the **antigen** to prepare the compsn.

Dwg.0/3

L8 ANSWER 36 OF 58 TOXLIT

AN 1994:22750 TOXLIT

DN CA-120-002261F

TI Cloning and expression of high molecular weight surface proteins of non-typeable *Haemophilus*.

AU Barenkamp SJ

SO (1993). PCT Int. Appl. PATENT NO. 93 19090 09/30/93.

CY United States

DT Patent

FS CA

LA English

OS CA 120:2261

EM 199405

AB The genes for high mol. wt. surface proteins

HMW1 and 2 of *H. influenzae* are cloned and

sequenced. The amino acid sequences of HMW1 and 2 derived from the genes had high homol. with that of the filamentous hemagglutinin of *Bordetella pertussis*. The HMW1 and 2 are useful for prepn. of protective **antigens** against nontypeable

*Haemophilus*-assocd. diseases such as otitis, sinusitis, bronchitis, etc., and as carrier for the protective Hib carrier polysaccharides in a conjugate vaccine against meningitis. The genes for the high mol. wt. surface proteins were cloned from a genomic library of *H. influenzae* constructed on

Searcher : Shears 308-4994

lambdaEMBL3 by immunol. screening using an human antibody against the **high** mol. wt. surface proteins. Also shown was the adherence of the HMW1 and 2 on the Chang epithelial cells. HMW3 and 4 were also cloned and partially sequenced.

L8 ANSWER 37 OF 58 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.  
 AN 93346827 EMBASE  
 DN 1993346827  
 TI Formation of the K30 (group I) capsule in Escherichia coli O9:K30 does not require attachment to lipopolysaccharide lipid A-core.  
 AU MacLachlan P.R.; Keenleyside W.J.; Dodgson C.; Whitfield C.  
 CS Department of Microbiology, University of Guelph, Guelph, Ont. N1G 2W1, Canada  
 SO Journal of Bacteriology, (1993) 175/23 (7515-7522).  
 ISSN: 0021-9193 CODEN: JOBAAY  
 CY United States  
 DT Journal; Article  
 FS 004 Microbiology  
 LA English  
 SL English  
 AB Escherichia coli K **antigens** (capsular polysaccharides) are divided into two broad classes, designated groups I and II, on the basis of a number of chemical, physical, and genetic criteria. Group I K **antigens** can be further subdivided on the basis of the absence (group IA) or presence (group IB) of amino sugars in the repeating unit of the K **antigen**. One criterion proposed for inclusion in group I is covalent linkage of the capsular polysaccharide to the lipid A-core of lipopolysaccharide (LPS). E. coli O9:K30 is a strain with a representative group IA K **antigen**. This organism synthesizes an LPS-associated low-molecular-weight form of K30 **antigen** which is called K(LPS). To determine the involvement of LPS lipid A-core in expression of the K30 capsular polysaccharide, E. coli K30/K-12 hybrid strains were constructed with mutations in the E. coli K-12 rfa locus, responsible for the biosynthesis of the LPS core oligosaccharide. These strains lack K(LPS), indicating that a full-length core is required for K(LPS) expression. However, formation of a K30 capsule was unaffected by rfa defects, indicating that attachment to lipid A-core is not an obligatory step for either export of **high-molecular-weight** capsular polysaccharide or maintenance of the capsular structure on the cell surface. Silver-stained tricine-sodium dodecyl sulfate-polyacrylamide gel electrophoresis profiles of lipopolysaccharides from other E. coli K serotypes showed that all strains with group IB K **antigens** expressed some K(LPS). In contrast, some strains with group IA K **antigens** appear to lack K(LPS). Consequently, although association of group I K **antigens** with lipid A-core is common, it is not a universal marker for inclusion in group I.

Searcher : Shears 308-4994

DUPLICATE 18

L8 ANSWER 38 OF 58 MEDLINE

AN 94041638 MEDLINE

DN 94041638

TI Outer membrane protein binding sites of complement component 3 during opsonization of *Haemophilus influenzae*.

AU Hetherington S V; Patrick C C; Hansen E J

CS Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, Tennessee 38101-0318..

NC P30 OCA 21765 (NCRR)

2 SO7 RR 05584-24

SO INFECTION AND IMMUNITY, (1993 Dec) 61 (12) 5157-63.

Journal code: GO7.-ISSN: 0019-9567.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

OS GENBANK-J03381; GENBANK-J03359; GENBANK-M19391

EM 199402

AB Complement component 3 (C3) binding to *Haemophilus influenzae* type b (Hib) is an important step in host defense against invasive disease, but the details of this process remain poorly understood. We have shown that the P1 and P2 outer membrane proteins (OMPs) serve as binding sites for C3 on serum-opsonized Hib. Whole-cell lysates of opsonized Hib were subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis, and the resolved proteins were transferred to nitrocellulose. Immunoblot analysis with monoclonal antibodies (MAbs) to the 49-kDa P1 and 39-kDa P2 OMPs demonstrated high-molecular-weight bands that were not present when the bacteria were opsonized with heat-inactivated or methylamine-treated serum. Immunoblot analysis with MAbs to the 98- or 16-kDa (P6) OMPs did not reveal additional bands. An unencapsulated Hib mutant still lacked C3 bound to the 98-kDa or P6 OMP, indicating that the absence of C3 binding to these proteins was not the result of epitope masking by the capsule. Studies with MAbs to C3 fragments confirmed that the anti-P1- and anti-P2-reactive bands were C3 fragments bound to these OMPs. The molecular weights of proteins reactive to anti-OMP and anti-C3 antibodies indicated that multiple C3 fragments may be bound to P1 or that C3 may be bound to P2 multimers. Finally, the presence of other anti-C3-reactive proteins indicated that several other proteins serve as C3 targets during the opsonization of Hib.

L8 ANSWER 39 OF 58 BIOSIS COPYRIGHT 1999 BIOSIS

AN 1993:501112 BIOSIS

DN PREV199396125119

TI Characterisation of *Plesiomonas shigelloides* strains that share type-specific antigen with *Shigella flexneri* 6 and common group 1 antigen with *Shigella flexneri* spp. and *Shigella*

Searcher : Shears 308-4994



- dysenteriae 1.
- AU Albert, M. J. (1); Ansaruzzaman, M.; Qadri, F.; Hossain, A.;  
Kibriya, A. K. M. G.; Haider, K.; Nahar, S.; Faruque, S. M.; Alam,  
A. N.
- CS (1) Lab. Sci. Div., ICDDR, B, G.P.O. Box 128, Dhaka 1000 Bangladesh
- SO Journal of Medical Microbiology, (1993) Vol. 39, No. 3, pp. 211-217.  
ISSN: 0022-2615.
- DT Article
- LA English
- AB Three strains of *Plesiomonas shigelloides* isolated from patients  
with diarrhoea were agglutinated with *Shigella flexneri* 6 antiserum  
in slide and tube tests. All the strains were also agglutinated with  
a monoclonal antibody to the common group 1 antigen shared  
between *S. flexneri* serotypes and *S. dysenteriae* type 1. Further  
studies with one strain also showed sharing of antigenicity in an  
enzyme-linked immunosorbent assay. The results suggest that the  
strains share type-specific antigen with *S. flexneri* 6 and  
the common group 1 antigen with *S. flexneri* serotypes and  
*S. dysenteriae* 1. The sharing of antigens may have  
implications for cross-protection. One strain adhered to HEp-2 cell  
monolayers. None of the strains contained high mol.  
wt plasmids and there was no sequence homology with the  
invasiveness plasmid of *Shigella* spp. in DNA probe hybridization.  
They were susceptible to the commonly used antibiotics. However,  
they possessed four other virulence-associated properties of  
*Shigella* spp. that included Congo-red binding, hydrophobicity,  
toxicity to HeLa cells and Hep-2 cell invasiveness (although they  
gave negative results in the Sereny test for invasiveness). These  
data suggest that the three unique strains might be considered  
pathogenic. Studies in animal models and human volunteers would be  
necessary to establish their pathogenic potential.
- L8 ANSWER 40 OF 58 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 19
- AN 1993:292934 BIOSIS
- DN PREV199345011059
- TI The ANWJ blood group antigen *Haemophilus*  
*influenzae* receptor resides on a high-molecular-  
weight protein expressed by CD44 transfectants.
- AU Telen, M. J.; Rao, N.; Udani, M.; Liao, H.-X.; Haynes, B. F.
- CS Duke Univ. Med. Center, Durham, NC USA
- SO Clinical Research, (1993) Vol. 41, No. 2, pp. 161A.  
Meeting Info.: Joint Meeting of the Association of American  
Physicians, the American Society for Clinical Investigation, and the  
American Federation for Clinical Research Washington, DC, USA April  
30-May 3, 1993  
ISSN: 0009-9279.
- DT Conference
- LA English

L8 ANSWER 41 OF 58 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD  
 AN 92-058283 [08] WPIDS  
 TI New immunogenic conjugate - comprises antigen bound to filamentous haemagglutinin of Bordetella pertussis, used as carrier for conjugate vaccines.  
 DC B04 D16  
 IN COWELL, J L; DICK, W E; KIMURA, A  
 PA (AMCY) AMERICAN CYANAMID CO  
 CYC 18  
 PI EP 471177 A 920219 (9208)\*  
 R: AT BE CH DE ES FR GB GR IT LI NL SE  
 NO 9103130 A 920214 (9216)  
 AU 9181789 A 920220 (9218)  
 CA 2048917 A 920214 (9218)  
 FI 9103820 A 920214 (9219)  
 JP 04230634 A 920819 (9241) 7 pp  
 EP 471177 A3 930224 (9348)  
 AU 649700 B 940602 (9427)  
 EP 471177 B1 951004 (9544) EN 9 pp  
 R: AT BE CH DE DK ES FR GB GR IT LI NL SE  
 DE 69113564 E 951109 (9550)  
 ADT EP 471177 A EP 91-110919 910702; FI 9103820 A FI 91-3820 910812; JP 04230634 A JP 91-222392 910808; EP 471177 A3 EP 91-110919 910702; AU 649700 B AU 91-81789 910812; EP 471177 B1 EP 91-110919 910702; DE 69113564 E DE 91-613564 910702, EP 91-110919 910702  
 FDT AU 649700 B Previous Publ. AU 9181789; DE 69113564 E Based on EP 471177  
 PRAI US 90-565161 900813  
 AN 92-058283 [08] WPIDS  
 AB EP 471177 A UPAB: 940120

An immunogenic conjugate comprises an antigen coupled to a filamentous haemagglutinin (FHA) of Bordetella pertussis or its immunologically active fragment, or to an immunologically cross-reactive mutant FHA of B pertussis or its portion.

Also claimed is an immunogenic conjugate comprising polyribosylribitolphosphate (PRRP) coupled to a FHA of B pertussis or its immunologically active portion, or to an immunologically cross-reactive mutant of FHA of B pertussis or its portion. The antigen is a carbohydrate e.g. a bacterial capsular oligosaccharide or polysaccharide or their fragments, esp. from H. influenza, Streptococcus pneumoniae, Neisseria meningitidis, Klebsiella pneumoniae, Pseudomonas aeruginosa and Staphylococcus aureus, and is pref. PRRP.

USE/ADVANTAGE - The conjugates are used as a vaccine, and for treatment and prophylaxis of e.g. AIDs and post-exposure conditions. FHA acts as a carrier for antigens, e.g. bacteria, viruses and cellular microcomponents, as it is nontoxic, has a relatively high mol. wt. and after conjugation with antigens retains both T- and B-cell epitopes. FHA may also

Searcher : Shears 308-4994

help to protect against marginally or non-immunogenic antigens when they are conjugated to FHA. When the antigen is (PRRP) of *Haemophilus influenzae* type P the vaccine is against meningitis. Admin. is intradermal, transdermal (e.g. by slow release polymers) intramuscular, intraperitoneal, intravenous, subcutaneous, oral and intranasal. @ (8pp Dwg.No.0/0

ABEQ EP 471177 A UPAB: 940120

An immunogenic conjugate comprises an antigen coupled to a filamentous haemagglutinin (FHA) of *Bordetella pertussis* or its immunologically active fragment, or to an immunologically cross-reactive mutant FHA of *B pertussis* or its portion.

Also claimed is an immunogenic conjugate comprising polyribosylribitolphosphate (PRRP) coupled to a FHA of *B pertussis* or its immunologically active portion, or to an immunologically cross-reactive mutant of FHA of *B pertussis* or its portion. The antigen is a carbohydrate e.g. a bacterial capsular oligosaccharide or polysaccharide or their fragments, esp. from *H. influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, and is pref. PRRP.

USE/ADVANTAGE - The conjugates are used as a vaccine, and for treatment and prophylaxis of e.g. AIDs and post-exposure conditions. FHA acts as a carrier for antigens, e.g. bacteria, viruses and cellular microcomponents, as it is nontoxic, has a relatively high mol. wt. and after conjugation with antigens retains both T- and B-cell epitopes. FHA may also help to protect against marginally or non-immunogenic antigens when they are conjugated to FHA. When the antigen is (PRRP) of *Haemophilus influenzae* type P the vaccine is against meningitis. Admin. is intradermal, transdermal (e.g. by slow release polymers) intramuscular, intraperitoneal, intravenous, subcutaneous, oral and intranasal. @ (8pp Dwg.No.0/0

ABEQ EP 471177 B UPAB: 951109

An immunogenic conjugate, comprising an antigen coupled to a filamentous hemagglutinin of *Bordetella pertussis* or an immunologically active portion thereof, or to an immunologically cross-reactive mutant filamentous hemagglutinin of *Bordetella pertussis* or portion thereof.  
Dwg.0/0

L8 ANSWER 42 OF 58 MEDLINE

DUPLICATE 20

AN 92268652 MEDLINE

DN 92268652

TI Outer membrane proteins and lipopolysaccharides of nontypeable *Haemophilus influenzae*.

AU Barenkamp S J

CS Edward Mallinckrodt Department of Pediatrics, Washington University  
Searcher : Shears 308-4994

09/210995

School of Medicine, St. Louis, Missouri..

NC AI-21707 (NIAID)

SO JOURNAL OF INFECTIOUS DISEASES, (1992 Jun) 165 Suppl 1 S181-4. Ref:  
12

Journal code: IH3. ISSN: 0022-1899.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 199208

AB Several outer-membrane proteins of nontypeable *Haemophilus influenzae* are potential vaccine candidates: P2 and P6 elicit antibodies that are bactericidal and protective in experimental models of infection. Other proteins are being investigated. A group of surface-exposed high-molecular-weight proteins that are major targets of antibody in human convalescent sera were identified. Monoclonal antibodies to the high-molecular-weight proteins of a prototype strain recognized two distinct but related proteins and were bactericidal for the prototype strain and other strains that shared the epitope recognized by the monoclonals. Genes encoding the two proteins in the prototype strain recognized by the monoclonals were cloned and sequenced. The sequences were distinct but related, and the derived amino acid sequences had sequence similarity to that of filamentous hemagglutinin of *Bordetella pertussis*, an important adherence factor and protective antigen.

L8 ANSWER 43 OF 58 BIOSIS COPYRIGHT 1999 BIOSIS

AN 1992:316953 BIOSIS

DN BR43:17678

TI HIGH MOLECULAR WEIGHT HMW  
PROTEINS OF NONTYPABLE *HAEMOPHILUS-INFLUENZAE*  
NTHI MEDIATE ATTACHMENT TO HUMAN EPITHELIAL CELLS.

AU ST GEME J W III; FALKOW S; BARENKAMP S J

CS STANFORD UNIV. SCH. MED., DEP. MICROBIOL. IMMUNOL., STANFORD, CALIF.

SO MEETING OF THE AMERICAN PEDIATRIC SOCIETY AND THE SOCIETY FOR  
PEDIATRIC RESEARCH, BALTIMORE, MARYLAND, USA, MAY 4-7, 1992. PEDIATR  
RES. (1992) 31 (4 PART 2), 179A.  
CODEN: PEREBL. ISSN: 0031-3998.

DT Conference

FS BR; OLD

LA English

L8 ANSWER 44 OF 58 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 21

AN 1992:382914 BIOSIS

DN BR43:49864

TI A HIGH-MOLECULAR-WEIGHT OUTER MEMBRANE PROTEIN  
Searcher : Shears 308-4994

09/210995

THAT IS A POTENTIAL TARGET FOR PROTECTIVE IMMUNITY TO TYPE B AND  
UNTYPABLE **HAEMOPHILUS-INFLUENZAE**.

AU THOMAS W R; FLACK F S; CALLOW M G; CHUA K-Y  
CS WEST. AUST. RES. INST. CHILD HEALTH, GPO BOX D184, PERTH 6001, WEST.  
AUST., AUST.  
SO MEETING ON EPIDEMIOLOGY, PATHOGENESIS, AND PREVENTION OF HAEMOPHILUS  
INFLUENZAE DISEASE, VELDHOVEN, NETHERLANDS, SEPTEMBER 24-28, 1990. J  
INFECT DIS. (1992) 165 (SUPPL 1), S75-S76.  
CODEN: JIDIAQ. ISSN: 0022-1899.  
DT Conference  
FS BR; OLD  
LA English

L8 ANSWER 45 OF 58 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.  
AN 92175681 EMBASE  
DN 1992175681  
TI Outer membrane proteins and lipopolysaccharides of nontypeable  
**Haemophilus influenzae**.  
AU Barenkamp S.J.  
CS Department of Pediatrics, St. Louis University, School of Medicine,  
1465 S. Grand Blvd., St. Louis, MO 63104, United States  
SO Journal of Infectious Diseases, (1992) 165/SUPPL. 1 (S181-S184).  
ISSN: 0022-1899 CODEN: JIDIAQ  
CY United States  
DT Journal; General Review  
FS 004 Microbiology  
007 Pediatrics and Pediatric Surgery  
026 Immunology, Serology and Transplantation  
LA English  
SL English  
AB Several outer membrane proteins of nontypeable **Haemophilus**  
**influenzae** are potential vaccine candidates: P2 and P6  
elicit antibodies that are bactericidal and protective in  
experimental models of infection. Other proteins are being  
investigated. A group of surface-exposed **high-molecular-**  
**weight** proteins that are major targets of antibody in human  
convalescent sera were identified. Monoclonal antibodies to the  
**high-molecular-weight** proteins of a prototype  
strain recognized two distinct but related proteins and were  
bactericidal for the prototype strain and other strains that shared  
the epitope recognized by the monoclonals. Genes encoding the two  
proteins in the prototype strain recognized by the monoclonals were  
cloned and sequenced. The sequences were distinct but related, and  
the derived amino acid sequences had sequence similarity to that of  
filamentous hemagglutinin of *Bordetella pertussis*, an important  
adherence factor and protective **antigen**.

L8 ANSWER 46 OF 58 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.  
AN 92175647 EMBASE

Searcher : Shears 308-4994

09/210995

DN 1992175647  
TI A high-molecular-weight outer membrane protein  
that is a potential target for protective immunity to type b and  
untypeable *Haemophilus influenzae*.  
AU Thomas W.R.; Flack F.S.; Callow M.G.; Chua K.Y.  
CS WA Res. Inst. for Child Health, GPO Box D184, Perth, WA. 6001,  
Australia  
SO Journal of Infectious Diseases, (1992) 165/SUPPL. 1 (S75-S76).  
ISSN: 0022-1899 CODEN: JIDIAQ  
CY United States  
DT Journal; Article  
FS 004 Microbiology  
007 Pediatrics and Pediatric Surgery  
026 Immunology, Serology and Transplantation  
LA English

L8 ANSWER 47 OF 58 MEDLINE  
AN 90256277 MEDLINE  
DN 90256277  
TI Expression in *Escherichia coli* of a high-molecular-  
weight protective surface antigen found in  
nontypeable and type b *Haemophilus influenzae*.  
AU Thomas W R; Callow M G; Dilworth R J; Audesho A A  
CS Clinical Immunology Research Unit, Princess Margaret Hospital,  
Subiaco, Western Australia..  
SO INFECTION AND IMMUNITY, (1990 Jun) 58 (6) 1909-13.  
Journal code: GO7. ISSN: 0019-9567.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199008  
AB An *Escherichia coli* clone producing a high-molecular-  
weight surface antigen of *Haemophilus influenzae*  
*type b* (Hib) was isolated from a library of Hib  
DNA fragments cloned as lysogens in a lambda replacement vector. The  
antigen is found in sarcosyl-insoluble outer membrane  
protein preparations and was produced by all 36 *H. influenzae*  
isolates tested. Absorption studies indicated  
that the antigen is a surface determinant on all isolates  
tested. Antibodies to the antigen (D15) were found in  
eight of nine convalescent-phase sera from children with invasive  
Hib infection. Affinity-purified antibodies prepared against the  
cloned antigen gave protection against the development of  
bacteremia in a rat pup model.

L8 ANSWER 48 OF 58 MEDLINE  
AN 86113570 MEDLINE  
DN 86113570

DUPLICATE 22

Searcher : Shears 308-4994

09/210995

TI Inhibition of attachment of *Streptococcus pneumoniae* and  
*Haemophilus influenzae* by human milk and receptor  
oligosaccharides.  
AU Andersson B; Porras O; Hanson L A; Lagergard T; Svanborg-Eden C  
SO JOURNAL OF INFECTIOUS DISEASES, (1986 Feb) 153 (2) 232-7.  
Journal code: IH3. ISSN: 0022-1899.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Abridged Index Medicus Journals; Priority Journals  
EM 198605  
AB Human milk inhibited the attachment of *Streptococcus pneumoniae* and  
*Haemophilus influenzae* to human pharyngeal or  
buccal epithelial cells. Infant formulas and cow and buffalo milk  
showed a lower inhibitory activity against pneumococci and enhanced  
the adhesion of *H. influenzae*. The antiadhesive  
effect against *S. pneumoniae* was found in both the high- and the  
low-molecular-weight fractions of milk. The inhibitory activity in  
the high-molecular-weight fraction was  
independent of specific antibody content; it was present after  
immunoabsorption and in the milk from IgA-deficient women. The  
inhibitory activity in the low-molecular-weight fraction was in part  
explained by the content of oligosaccharides corresponding to the  
carbohydrate moieties of the neolactoseries of glycolipids, which  
have previously been shown to act as receptors for attaching  
pneumococci. The antiadhesive activity against *H.*  
*influenzae* was restricted to the high-molecular-  
weight fraction of the milk and was unaffected by  
immunoabsorption. Milk may protect against otitis by reducing  
colonization.

L8 ANSWER 49 OF 58 BIOTECHDS COPYRIGHT 1999 DERWENT INFORMATION LTD  
AN 86-07882 BIOTECHDS  
TI Cloning and expression of a gene encoding an immunogenic,  
extracellular protein of *Haemophilus influenzae*  
type b in *Escherichia coli*;  
application to vaccine production (conference abstract)  
AU Gonzales F R; Norgard M V; Kupersztoch J M; Hansen E J  
LO University of Texas Health Science Center at Dallas, Dallas, TX  
75235, U.S.A.  
SO Abstr.Annu.Meet.Am.Soc.Microbiol.; (1986) 86 Meet., 90, D-145  
DT Journal  
LA English  
AN 86-07882 BIOTECHDS  
AB *Haemophilus influenzae* type b (Hib) synthesizes  
a high mol.wt. (100,000) protein which is  
immunogenic in human infants with Hib meningitis. To facilitate  
genetic analysis of the 100K protein, genomic libraries containing  
Hib DNA were constructed in *Escherichia coli* HB101 using the  
Searcher : Shears 308-4994

cloning vehicle pBR322. More than 12,000 recombinant clones were screened in a colony blot-RIA using a murine monoclonal antibody directed against the Hib 100K protein. 10 Clones reactive with this monoclonal antibody contained a hybrid plasmid bearing an insert of approximately 13.5-kb of Hib DNA. Each recombinant clone synthesized a protein antigen with an apparent mol.wt. identical to that of the native Hib protein. (0 ref)

L8 ANSWER 50 OF 58 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.  
 AN 85147697 EMBASE  
 DN 1985147697  
 TI Composition and antigenic activity of the oligosaccharide moiety of *Haemophilus influenzae* type b lipooligosaccharide.  
 AU Inzana T.J.; Seifert Jr. W.E.; Williams R.P.  
 CS Department of Microbiology and Immunology, Baylor College of Medicine, Houston, TX 77030, United States  
 SO Infection and Immunity, (1985) 48/2 (324-330).  
 CODEN: INFIBR  
 CY United States  
 DT Journal  
 FS 026 Immunology, Serology and Transplantation  
 004 Microbiology  
 LA English  
 AB The oligosaccharide moiety of the lipooligosaccharide of *Haemophilus influenzae* type b strain Eag was isolated from the lipid component by mild acid hydrolysis and purified by gel filtration. Fast atom bombardment-mass spectrometry indicated that the lipid-free oligosaccharide had a basic molecular weight of 1,768; polysaccharides comparable to high-molecular-weight O side chains were not found. Glucose, galactose, galactosamine, heptose, 3-deoxy-D-manno-2-octulosonic acid (KDO), ethanolamine, and phosphate were identified in the lipid-free oligosaccharide by colorimetric assays, gel chromatography-mass spectrometry, or an amino acid analyzer. The presence of KDO was not clearly established by a thiobarbituric acid assay or by growth inhibition by a diazaborine derivative thought to block KDO synthesis. However, the semicarbazide assay and gas chromatography-mass spectrometry confirmed the presence of KDO. Lectin precipitation by Eag lipooligosaccharide in gels indicated that .beta.-D-galactose was present and that some of this monosaccharide was a terminal, nonreducing residue linked to N-acetyl-D-galactosamine. The lipid-free oligosaccharide was antigenic and completely inhibited lipooligosaccharide antibody (predominantly immunoglobulin G [IgG] and IgM) in an enzyme-linked immunosorbent assay, whereas the solubilized lipid A moiety did not. *H. influenzae* type b lipid-free oligosaccharide differed from core oligosaccharide of *Salmonella* lipooligosaccharide by the presence of galactosamine and a smaller percentage of heptose and KDO.



DUPLICATE 23

L8 ANSWER 51 OF 58 MEDLINE

AN 85078580 MEDLINE

DN 85078580

TI A minor high-molecular-weight outer membrane protein of *Haemophilus influenzae* type b is a protective antigen.

AU Kimura A; Gulig P A; McCracken G H Jr; Loftus T A; Hansen E J

NC AI-17621 (NIAID)

AI-17012 (NIAID)

SO INFECTION AND IMMUNITY, (1985 Jan) 47 (1) 253-9.  
Journal code: G07. ISSN: 0019-9567.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 198504

AB Cell surface-exposed antigenic determinants of several high-molecular-weight outer membrane proteins of *Haemophilus influenzae* type b (Hib) have been shown to be consistently immunogenic in human infants convalescing from Hib meningitis. A monoclonal antibody (mab), 6G12, directed against one of these cell surface-exposed outer membrane proteins that has an apparent molecular weight of 98,000 (98K) was identified by radioimmunoprecipitation analysis. Of 120 clinical isolates of Hib, 83 were found to possess antigenic determinants which reacted with mab 6G12 in a colony blot-radioimmunoassay procedure, indicating that the antigenic determinant recognized by mab 6G12 is present in the majority of Hib strains. A different radioimmunoassay, which uses whole Hib cells as antigen, confirmed that strains reactive with mab 6G12 in the colony blot-radioimmunoassay procedure possessed a cell surface-exposed and antibody-accessible antigenic determinant recognized by this mab. Hib strains which did not react with mab 6G12 were found to lack a 98K protein. Passive immunization with mab 6G12 reduced the level of bacteremia that developed in infant rats challenged with the homologous Hib strain against which this mab was raised. In contrast, no protection was observed when the challenge strain was one which lacks the antigenic determinant recognized by mab 6G12. Radioimmunoprecipitation analysis of sera from human infants convalescing from Hib meningitis detected an antibody response directed against the 98K protein. The protection against experimental Hib disease provided by antibody to the 98K protein, the immunogenicity of this protein in human infants, and its presence in a majority of Hib strains indicate that the 98K outer membrane protein may have potential for vaccine development.

L8 ANSWER 52 OF 58 MEDLINE

AN 85071741 MEDLINE

Searcher : Shears 308-4994

09/210995

DN 85071741  
TI Complement in chronic secretory otitis media. C3  
breakdown and C3 splitting activity.  
AU Meri S; Lehtinen T; Palva T  
SO ARCHIVES OF OTOLARYNGOLOGY, (1984 Dec) 110 (12) 774-8.  
Journal code: 860. ISSN: 0003-9977.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Abridged Index Medicus Journals; Priority Journals  
EM 198503  
AB Occurrence of in vivo C3 breakdown and in vitro C3 splitting  
activity was studied in serum and middle-ear effusion (MEE) samples  
from 30 children with chronic secretory otitis  
media (SOM). The MEE showed strongly elevated levels of both  
low- and high-molecular-weight C3 breakdown  
products, along with decreased factor B, C4, and C3 levels. Total  
hemolytic complement component activity was virtually absent from  
MEE. The MEE fluids were found to contain C3 splitting factors as  
demonstrated by their high capacity to convert C3 in vitro from  
fresh normal human serum. This activity was not inhibited by the  
classic complement pathway inhibitor, 0.01M ethylene glycol  
tetra-acetic acid with 0.005M magnesium chloride. The results  
suggest that a strong local complement activation has taken place  
and that the factors responsible are present in the MEE of patients  
with SOM.

L8 ANSWER 53 OF 58 BIOSIS COPYRIGHT 1999 BIOSIS  
AN 1984:100652 BIOSIS  
DN BR27:17144  
TI IDENTIFICATION OF AN IMMUNOGENIC HIGH MOLECULAR  
WEIGHT OUTER MEMBRANE PROTEIN OF HAEMOPHILUS-  
INFLUENZAE TYPE B AS A PROTECTIVE ANTIGEN.  
AU KIMURA A; MCCracken G H JR; GULIG P A; LOFTUS T A; HANSEN E J  
CS UNIV. TEX. HEALTH SCI. CENT., DALLAS, TEX.  
SO 84TH ANNUAL MEETING OF THE AMERICAN SOCIETY FOR MICROBIOLOGY, ST.  
LOUIS, MO., USA, MAR. 4-9, 1984. ABSTR ANNU MEET AM SOC MICROBIOL.  
(1984) 84 (0), ABSTRACT B99.  
CODEN: ASMACK. ISSN: 0094-8519.  
DT Conference  
FS BR; OLD  
LA English

L8 ANSWER 54 OF 58 MEDLINE  
AN 77251039 MEDLINE  
DN 77251039  
TI Immunogenicity in weanling rabbits of a polyribophosphate complex  
from Haemophilus influenzae type b.  
AU Anderson P; Smith D H

Searcher : Shears 308-4994

SO JOURNAL OF INFECTIOUS DISEASES, (1977 Aug) 136 Suppl S63-70.  
 Journal code: IH3. ISSN: 0022-1899.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Abridged Index Medicus Journals; Priority Journals  
 EM 197712  
 AB Polyribophosphate (PRP), the capsular polysaccharide of *Haemophilus influenzae* type b, is more effectively immunogenic when it is associated with the bacterium than when it is in the purified form that is being tested as a vaccine for humans. In an effort to analyze this difference, we isolated from *H. influenzae* type b a high-molecular-weight, soluble complex, in which PRP appears to be combined with protein (about 7% protein). The pyrogenicity and limulus lysate gelation activity of the complex suggest that a small amount of lipopolysaccharide also is present. The protein was resolved into five polypeptides by electrophoresis in polyacrylamide gel containing sodium dodecyl sulfate. In weanling rabbits, which do not respond to purified PRP, the complex induces high titers of antibody of PRP, in an anamnestic pattern. Bactericidal antibody to other bacterial components was also elicited. Equilibrium density gradient centrifugation of the complex indicated that most of the immunogenicity of PRP resides in the least dense fractions, which are high in protein, low in polysaccharide, and active in the limulus lysate test; denser fractions that react strongly with limulus lysate but are poor in protein were much less immunogenic.

L8 ANSWER 55 OF 58 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.  
 AN 78171986 EMBASE  
 DN 1978171986  
 TI Immunogenicity in weanling rabbits of a polyribophosphate complex from *Haemophilus influenzae* type b.  
 AU Anderson P.; Smith D.H.  
 CS Infect. Dis. Div., Child Hosp. Med. Cent., Boston, Mass., United States  
 SO Journal of Infectious Diseases, (1977) 136/2 Suppl. (S63-S70).  
 CODEN: JIDIAQ  
 CY United States  
 DT Journal  
 FS 004 Microbiology  
 026 Immunology, Serology and Transplantation  
 LA English  
 AB Polyribophosphate (PRP), the capsular polysaccharide of *Haemophilus influenzae* type b, is more effectively immunogenic when it is associated with the bacterium than when it is in the purified form that is being tested as a vaccine for humans. In an effort to analyze this difference, we isolated from *H. influenzae* type b a high-molecular-weight, soluble complex, in which PRP appears to be combined with protein (about 7% protein). The pyrogenicity and limulus lysate gelation activity of the complex suggest that a small amount of lipopolysaccharide also is present. The protein was resolved into five polypeptides by electrophoresis in polyacrylamide gel containing sodium dodecyl sulfate. In weanling rabbits, which do not respond to purified PRP, the complex induces high titers of antibody of PRP, in an anamnestic pattern. Bactericidal antibody to other bacterial components was also elicited. Equilibrium density gradient centrifugation of the complex indicated that most of the immunogenicity of PRP resides in the least dense fractions, which are high in protein, low in polysaccharide, and active in the limulus lysate test; denser fractions that react strongly with limulus lysate but are poor in protein were much less immunogenic.

Searcher : Shears 308-4994

weight, soluble complex, in which PRP appears to be combined with protein (about 7% protein). The pyrogenicity and limulus lysate gelation activity of the complex suggest that a small amount of lipopolysaccharide also is present. The protein was resolved into five polypeptides by electrophoresis in polyacrylamide gel containing sodium dodecyl sulfate. In weanling rabbits, which do not respond to purified PRP, the complex induces high titers of antibody to PRP, in an anamnestic pattern. Bactericidal antibody to other bacterial components was also elicited. Equilibrium density gradient centrifugation of the complex indicated that most of the immunogenicity of PRP resides in the least dense fractions, which are high in protein, low in polysaccharide, and active in the limulus lysate test; denser fractions that react strongly with limulus lysate but are poor in protein were much less immunogenic.

L8 ANSWER 56 OF 58 MEDLINE

DUPLICATE 24

AN 76266429 MEDLINE

DN 76266429

TI [Experimental studies on the reaction of the immunological system during chronic otitis media and about the course of this disease (author's transl)].

Experimentelle Untersuchungen zum Verhalten des Immunsystems bei der chronischen Mittelohreiterung und zum Verlauf dieses Krankheitsbildes.

AU Kastenbauer E R; Hochstrasser K

SO LARYNGOLOGIE, RHINOLOGIE, OTOLOGIE, (1976 Jan) 55 (1) 36-42.  
Journal code: L1R. ISSN: 0340-1588.

CY GERMANY, WEST: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA German

FS Priority Journals

EM 197612

AB During chronic otitis media intact

immunoglobulins are split due to the proteolytic activity of extracellular bacterial proteinases into fragments of different molecular weight. The most malignant bacterial proteinases are the proteinases of pseudomonas aeruginosa (pyrocyanus). These proteinases can only be inhibited by alpha-2-macroglobulin of human blood serum. Because of its high molecular weight we find this inhibitor only in a very low concentration in the middle ear secretion. The destruction of the immunoglobulins is certainly one of the factors of weakening the immunological system in the middle ear. The inhibitory system with alpha-1-antitrypsin, inter-alpha-trypsin inhibitor and alpha-1-antichymotrypsin is unable to inhibit these bacterial proteinases of pseudomonas aeruginosa. The only possibility to get a high concentration of alpha-2-macroglobulin in the middle ear secretion is the liberation of this inhibitory by injuring blood vessels during a tympanoplasty. By this procedure the proteinases of pseudomonas aeruginosa with

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maximum activity at pH 7.8 and with a high proteolytic activity are almost completely inhibited. By blocking these proteinases combined with an appropriate antibiotic therapy and with the reconstruction of the destroyed parts of the middle ear by a tympanoplasty we can produce a preponderance of the immunological system as compared with the proteolytic activity of the proteinases. This high proteolytic activity can be a cause of the destruction of the small processes of the ossicular bones, especially of the lenticular process of incus. In order to demonstrate that there are proteolytic splitting processes of intact immunoglobulins, a quantitative analysis of the immunoglobulins IgG, IgA and IgM was done pre- and postoperatively. By these studies we found postoperatively a much higher level of intact immunoglobulins, particularly in cases of chronic **otitis media** associated with cholesteatoma. The blocking of the proteinases and the increase of the level of intact immunoglobulins combined with the reconstruction of physiological conditions in the chronically inflamed middle ear by a tympanoplasty lead to a stabilisation of the immunological and inhibitory system and create the prerequisites for a healing process in chronic **otitis media**. It is the purpose of further studies to learn about the capability of the split-products of the immunoglobulins to attach and to absorb **antigens** and toxins during a chronic inflammation in the middle ear.

L8 ANSWER 57 OF 58 MEDLINE DUPLICATE 25  
 AN 75155226 MEDLINE  
 DN 75155226  
 TI [Enzymatic and immunological inflammatory reactions in the middle ear (author's transl)].  
 Enzymatische und immunologische Entzündungsreaktionen im Mittelohr.  
 AU Kastenbauer E R  
 SO LARYNGOLOGIE, RHINOLOGIE, OTOLOGIE, (1975 Mar) 54 (3) 177-82.  
 Journal code: L1R. ISSN: 0340-1588.  
 CY GERMANY, WEST: Germany, Federal Republic of  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA German  
 FS Priority Journals  
 EM 197509  
 AB During chronic **otitis media** intact immunoglobulins are split by extracellular bacterial proteinases into fragments of different molecular weight, The most malignant extracellular proteinases with the greatest proteolytic activity against intact immunoglobulins are the bacterial proteinases of *Pseudomonas aeruginosa*. These proteinases cannot be inhibited by the other serum proteinase-inhibitor except for Alpha-2-Macroglobulin of the human blood serum. This inhibitor has a very high molecular weight, so that we cannot find it in a higher concentration in the middle-ear-secretory. We can liberate this inhibitor by injuring the blood vessels during a tympanoplasty. In  
 Searcher : Shears 308-4994

this way we get an inhibitory effect against these proteinases and combined with an appropriate antibiotic therapy we can cure a chronic otitis MEDIA. In order to demonstrate that there are immunological reactions in the middle ear against homografted ossicles, various transplantation with homologous ossicles have been performed between two inbreeding rat strains. After sensitisation of the host animals against antigens of the donor animals with skin grafts a reliable histologic infiltration with plasma cells and lymphocytes and the rejection of the graft could be insured. After a simple homologous transplantation without sensitisation, these rejection reactions occur only rarely and in a diminished form. Cialit storage of middle ear ossicles decreases the solubility of the contained proteins and this in turn diminishes the antigenicity, the amount the antigens, or it retards their liberation. It is for these reasons that Cialit-stored ossicles are more slowly transformed, and there are less inflammatory reactions and adhesions than with untreated ones. The osteogenetic capability of the ossicles is not affected by the Cialit storage.

L8 ANSWER 58 OF 58 CONFSCI COPYRIGHT 1999 CSA  
 AN 84:494 CONFSCI  
 DN 84006161  
 TI Identification of an immunogenic, high-molecular-weight outer membrane protein of *Haemophilus influenzae* type b as a protective antigen  
 AU Kimura, A.; McCracken, G.H., Jr.; Gulig, P.A.; Loftus, T.A.; Hansen, E.J.  
 CS Univ. Texas Health Sci. Cent., Dallas  
 SO Abstracts available: American Society for Microbiology, Publications Department, 1913 I St. NW, Washington, DC 20006, USA, Paper No. B99.  
 Meeting Info.: 841 0195: American Society for Microbiology 84th Annual Meeting (8410195). St. Louis, MO (USA). 4-9 Mar 84. American Society for Microbiology (ASM).  
 DT Conference  
 FS DCCP  
 LA UNAVAILABLE

FILE 'REGISTRY' ENTERED AT 12:46:30 ON 25 MAR 1999  
 E ALUMINUM HYDROXIDE/CN 5

L9 332 SEA ABB=ON PLU=ON (ALUMINUM HYDROXIDE ? OR ALUMINUM PHOSPHATE ?)/CN

FILE 'CAPLUS' ENTERED AT 12:47:03 ON 25 MAR 1999

L10 17 SEA ABB=ON PLU=ON L1 AND (L9 OR (AL OR ALUMIN?) (W) (PHOSPHATE OR PO# OR HYDROXIDE OR OH) OR ALPO# OR ALOH)  
 L11 16 SEA ABB=ON PLU=ON L10 NOT L3

Searcher : Shears 308-4994

claim 19

09/210995

L11 ANSWER 1 OF 16 CAPLUS COPYRIGHT 1999 ACS  
AN 1998:106016 CAPLUS  
DN 128:176969  
TI The NucA protein of *Haemophilus influenzae* and  
its gene sequence and use as a vaccine  
IN Zagursky, Robert John; Jones, Kevin Frederick; Ooi, Peggy  
PA American Cyanamid Company, USA; Zagursky, Robert John; Jones, Kevin  
Frederick; Ooi, Peggy  
SO PCT Int. Appl., 117 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9804703	A1	19980205	WO 97-US12790	19970723
	W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ZW				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2232975	AA	19980205	CA 97-2232975	19970723
	AU 9738077	A1	19980220	AU 97-38077	19970723
	EP 854925	A1	19980729	EP 97-935048	19970723
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRAI	US 96-22619		19960726		
	US 96-687865		19960726		
	WO 97-US12790		19970723		
AB	A protein from <i>H. influenzae</i> designated NucA is isolated and purified. The NucA protein has the amino acid sequence of 603 amino acid residues, or a biol. equiv. amino acid sequence. Amino acids 1-25 of NucA are the signal peptide, which is cleaved during processing of the mature protein. The NucA protein has a mol. wt. of .apprx.63 kDa as measured on a 12 % SDS-PAGE gel and possesses 5'-nucleotidase activity. The NucA protein is obtained by isolation and purifn. from the <i>H. influenzae</i> organism, by chem. synthesis, or by recombinant expression by an isolated and purified nucA DNA sequence which encodes the NucA protein. Such a DNA sequence hybridizes under std. high stringency Southern hybridization conditions with a DNA sequence encoding the NucA protein of <i>H. influenzae</i> having the amino acid sequence of the mature protein or a biol. equiv. amino acid sequence. The NucA protein is used to prep. a vaccine compn. which elicits a protective immune response in a mammalian host to protect the host against disease caused by <i>H. influenzae</i>				

IT 7784-30-7, Aluminum phosphate

Searcher : Shears 308-4994

09/210995

21645-51-2, Aluminum hydroxide,  
biological studies

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(adjuvant; NucA protein of *Haemophilus*  
*influenzae* and its gene sequence and use as a vaccine)

L11 ANSWER 2 OF 16 CAPLUS COPYRIGHT 1999 ACS

AN 1998:55553 CAPLUS

DN 128:127079

TI Multivalent DTP-polio vaccines

IN Fahim, Raafat E. F.; Tan, Larry U. L.; Barreto, Luis; Thippawong,  
John; Jackson, Gail E. D.

PA -- Connaught Laboratories Ltd., Can.; Fahim, Raafat E. F.; Tan, Larry  
U. L.; Barreto, Luis; Thippawong, John; Jackson, Gail E. D.

SO PCT Int. Appl., 117 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9800167	A1	19980108	WO 97-CA472	19970702
	W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			

AU 9732516 A1 19980121 AU 97-32516 19970702

PRAI US 96-672530 19960702

WO 97-CA472 19970702

AB A multi-component vaccine compn. is described comprising acellular pertussis vaccine components, diphtheria toxoid, tetanus toxoid, and inactivated poliovirus. The compn. also may contain a conjugate of a capsular polysaccharide of *Haemophilus influenzae* type b and tetanus toxoid or diphtheria toxoid, which may be reconstituted from a lyophilized state by the other components of the vaccine. The administration of the multiple component vaccine results in no diminution in the immunogenicity of any component as a result of interference by other components of the vaccine.

IT 7784-30-7, Aluminum phosphate  
21645-51-2, Aluminum hydroxide,  
biological studies

RL: BAC (Biological activity or effector, except adverse); THU  
(Therapeutic use); BIOL (Biological study); USES (Uses)

(prepn., immunogenicity, safety, and clin. effects of multivalent

Searcher : Shears 308-4994



09/210995

vaccines against pertussis, diphtheria, tetanus, poliomyelitis,  
and **Haemophilus influenzae** infection in  
children in relation to)

L11 ANSWER 3 OF 16 CAPLUS COPYRIGHT 1999 ACS

AN 1998:1387 CAPLUS

DN 128:74301

TI Monovalent pertussis vaccine and multivalent vaccines against  
hepatitis and Hib using pertactin

IN Slaoui, Moncef Mohamed; Stephenne, Jean

PA Smithkline Beecham Biologicals S.A., Belg.; Slaoui, Moncef Mohamed;  
Stephenne, Jean

SO PCT Int. Appl., 19 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9746255	A2	19971211	WO 97-EP2956	19970529
	WO 9746255	A3	19980108		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,  
DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP,  
KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,  
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT,  
UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR,  
GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM,  
GA, GN, ML, MR, NE, SN, TD, TG

AU 9731736 A1 19980105 AU 97-31736 19970529

PRAI GB 96-11501 19960603

WO 97-EP2956 19970529

AB Vaccine compns. comprising the 69K outer membrane protein of B.  
pertussis (pertactin) having 10-100 .mu.g of 69K per 0.5 mL dose are  
described for the treatment of whooping cough. Also described are  
combination vaccines comprising 10-100 .mu.g of 69K per 0.5 mL, esp.  
vaccines in which the 69K component is formulated with filamentous  
hemagglutinin (FHA) and pertussis toxoid (PT), optionally in  
combination with one or more other antigens such as hepatitis B  
surface antigen, **Haemophilus influenzae** b (Hib),  
injectable polio (IPV) and hepatitis A. Methods for prepg. the  
vaccines are described.

IT 7784-30-7, Aluminum phosphate

21645-51-2, Aluminum hydroxide, uses

RL: MOA (Modifier or additive use); USES (Uses)

(monovalent pertussis vaccine and multivalent vaccines against  
hepatitis and **Haemophilus influenza** type b  
using pertactin)

Searcher : Shears 308-4994

L11 ANSWER 4 OF 16 CAPLUS COPYRIGHT 1999 ACS

AN 1997:306965 CAPLUS

DN 127:3884

TI MF59 adjuvant enhances antibody responses of infant baboons immunized with *Haemophilus influenzae* type b and *Neisseria meningitidis* group C oligosaccharide-CRM197 conjugate vaccine

AU Granoff, Dan M.; McHugh, Yvonne E.; Raff, Howard V.; Mokatrin, Ahmad S.; Van Nest, Gary A.

CS Chiron Vaccines, Emeryville, CA, 94608, USA

SO Infect. Immun. (1997), 65(5), 1710-1715

CODEN: INFIBR; ISSN: 0019-9567

PB American Society for Microbiology-

DT Journal

LA English

AB The ability of the adjuvant MF59 to enhance the immunogenicity of polysaccharide-protein conjugate vaccines was investigated in infant baboons. MF59 consists of stable droplets (<250 nm) of the metabolizable oil squalene and two surfactants, polyoxyethylene sorbitan monooleate and sorbitan trioleate, in an oil-in-water emulsion. In humans, MF59 is well tolerated and enhances the immunogenicity of recombinant protein subunit or particle vaccines. Its effect on the immunogenicity of polysaccharide-protein conjugate vaccines is unknown. Baboons 1-4 mo of age were immunized i.m. with *N. meningitidis* group C and *H. influenzae* type b (Hib) oligosaccharide-CRM197 conjugate vaccines. The lyophilized vaccines were reconstituted with phosphate-buffered saline (PBS), Al(OH)<sub>3</sub> (alum), or MF59. Groups of 5 animals each were given 3 injections of the resp. formulations, with one injection every 4 wk. Four weeks after each immunization, the MF59 group had up to 7-fold-higher geometric mean anticapsular-antibody titers than the alum group and 5-10-fold higher *N. meningitidis* group C bactericidal antibody titers. Twenty-one weeks after the 3rd immunization, the MF59 group still showed 5-10-fold-higher anticapsular antibody titers. The antibody responses of the animals given the vaccines reconstituted with PBS were low at all times measured. Both the MF59 and alum groups, but not the PBS group, showed booster antibody responses to unconjugated Hib and *N. meningitidis* group C polysaccharides, results consistent with induction of memory B cells. Thus, MF59 may be useful for accelerating and augmenting immunity to polysaccharide-protein conjugate vaccines in infants.

L11 ANSWER 5 OF 16 CAPLUS COPYRIGHT 1999 ACS

AN 1997:145259 CAPLUS

DN 126:148484

TI Vaccine composition comprising a polysaccharide conjugate antigen adsorbed onto aluminum phosphate

IN Peetermans, Julien; Hauser, Pierre

Searcher : Shears 308-4994

09/210995

PA Smithkline Beecham Biologicals S.A., Belg.; Peetermans, Julien;  
Hauser, Pierre  
SO PCT Int. Appl., 15 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9700697	A1	19970109	WO 96-EP2690	19960619
	W:	AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, -LS, -LT, LU, -LV, -MD, MG, MK, MN, -MW, MX, -NO, NZ, PL, PT, RO, RU, SD, SE, SG			
	RW:	KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA			
	CA 2222455	AA	19970109	CA 96-2222455	19960619
	AU 9663591	A1	19970122	AU 96-63591	19960619
	AU 696338	B2	19980910		
	EP 833662	A1	19980408	EP 96-922871	19960619
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI			
	NO 9706035	A	19980216	NO 97-6035	19971222
PRAI	GB 95-12827		19950623		
	GB 95-13443		19950701		
	GB 95-25657		19951215		
	GB 96-6032		19960322		
	WO 96-EP2690		19960619		
AB	The invention relates to a vaccine formulation for the prevention of <i>Hemophilus influenzae</i> Type B (Hib) infections and where the antigen is adsorbed onto <b>aluminum phosphate</b> . The antigen is a capsular polysaccharide from <i>H. influenzae</i> B conjugate with a carrier protein. The carrier protein is Diphtheria toxoid, Diphtheria CRM197 protein, meningococcal outer membrane protein or Tetanus toxoid. The invention also relates to a multivalent vaccine.				
IT	<b>7784-30-7, Aluminum phosphate</b> RL: MOA (Modifier or additive use); USES (Uses) (vaccine compn. comprising polysaccharide conjugate antigen adsorbed onto)				
L11	ANSWER 6 OF 16 CAPLUS COPYRIGHT 1999 ACS				
AN	1996:548530 CAPLUS				
DN	125:177440				
TI	Immunogenic conjugate molecules				
IN	Yang, Yan-Ping; Kandil, Ali; Gisonni, Lucy; Fahim, Raafat E. F.; Klein, Michel H.				
PA	Connaught Laboratories Limited, Can.				
SO	PCT Int. Appl., 64 pp.				

Searcher : Shears 308-4994

09/210995

CODEN: PIXXD2

DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9621465	A2	19960718	WO 96-CA7	19960105
	WO 9621465	A3	19961010		
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN				
	US 5681570	A	19971028	US 95-371965	19950112
	CA 2210139	AA	19960718	CA 96-2210139	19960105
	AU 9643254	A1	19960731	AU 96-43254	19960105
	EP 805691	A2	19971112	EP 96-900066	19960105
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
PRAI	US 95-371965		19950112		
	WO 96-CA7		19960105		
AB	Immunogenic conjugate mols. comprising at least a portion of a capsular polysaccharide of a Streptococcus strain linked to at least a portion of an outer membrane protein of a Haemophilus strain are provided in which the immunogenicity of the capsular polysaccharide is increased. Particularly capsular polysaccharide from Streptococcus pneumoniae are linked to an outer membrane protein of a Haemophilus influenzae strain, which protein may be the P1, P2 or particularly the P6 outer membrane protein. Conjugate mols. comprising the P6 protein linked to a capsular polysaccharide from an encapsulated pathogen other than Streptococcus are also described, in which the immunogenicity of the capsular polysaccharide is enhanced. Such conjugate mols. may be incorporated into immunogenic compns. for protecting a host against disease caused by the Streptococcus strain and preferably also the Haemophilus strain. The conjugate mols. and antibodies specific for the capsular polysaccharide or specific for the outer membrane protein may be employed in diagnostic procedures and kits. A process for individually isolating P1, P2 and P6 outer membrane proteins from a Haemophilus strain is also provided.				
IT	7784-30-7, Aluminum phosphate 21645-51-2, Aluminum hydroxide, biological studies RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (immunoconjugates based on polysaccharide from Streptococcus and outer membrane protein from Haemophilus)				

Searcher : Shears. 308-4994

L11 ANSWER 7 OF 16 CAPLUS COPYRIGHT 1999 ACS  
 AN 1996:137694 CAPLUS  
 DN 124:173429  
 TI Adjuvant compositions comprising a mineral salt and another  
 immunostimulating compound  
 IN Kandil, Ali; James, Olive A.; Chong, Pele; Klein, Michel H.  
 PA Cannaught Laboratories Ltd., Can.  
 SO PCT Int. Appl., 54 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9534308	A2	19951221	WO 95-CA359	19950615
	WO 9534308	A3	19960523		
	W:		AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN		
	RW:		KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG		
	US 5837250	A	19981117	US 95-483856	19950607
	CA 2192659	AA	19951221	CA 95-2192659	19950615
	AU 9526670	A1	19960105	AU 95-26670	19950615
	EP 765163	A2	19970402	EP 95-921672	19950615
	R:		AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE		

PRAI US 94-261194 19940616  
 WO 95-CA359 19950615

OS MARPAT 124:173429

AB Adjuvant compns. for modulating an immune response to an antigen administered to a host comprise a mineral salt adjuvant and at least one other adjuvant. The compns. provide an adjuvanting effect on an antigen which is greater than the adjuvanting effect attainable by one of the adjuvants alone. An antigen is covalently bonded to a glycolipid analog to provide a discrete mol. which exhibits an enhanced adjuvanting effect on the antigen which is greater than the adjuvanting effect attainable in the absence of such covalent bonding. The antigen is microbial pathogens, bacteria, viruses, proteins, glycoproteins, lipoproteins, peptides, glycopeptides, toxoids, carbohydrates, tumor-specific antigens, etc. In example, synthetic peptides were prepd. as antigen, and N-(2-L-leucine-amino-2-deoxy-.beta.-D-glucopyranosyl)-N-octadecyldodecanamide acetate, tripalmityl-Cys-Ser-Ser-Asn-Ala, tripalmityl-Cys-Ser-Glu-Glu-Glu-Glu, tripalmityl-Cys-Ser-Lys-Lys-Lys-Lys, etc. were prepd. as adjuvant. Formulations contg. these synthetic antigen and adjuvants were prepd. as vaccines for HIV, flu, RSV, PIV3, flu BHA, pertussis

Searcher : Shears, 308-4994

toxoid, etc.

IT 7784-30-7, Aluminum phosphate  
21645-51-2, Aluminum hydroxide, uses  
RL: MOA (Modifier or additive use); USES (Uses)  
(adjuvant formulations contg. mineral salt and glycolipid or  
octadecyl ester of amino acid or lipoprotein)

L11 ANSWER 8 OF 16 CAPLUS COPYRIGHT 1999 ACS  
AN 1994:678850 CAPLUS  
DN 121:278850  
TI Vaccine compositions containing 3-O-deacylated monophosphoryl lipid  
A and adjuvant  
IN Hauser, Pierre; Voet, Pierre; Slaoui, Moncef; Garcon-Johnson,  
Nathalie Marie-Josephe Claude; Desmons, Pierre  
PA SmithKline Beecham Biologicals (S.A.), Belg.  
SO PCT Int. Appl., 46 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9421292	A1	19940929	WO 94-EP818	19940314
	W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2157376	AA	19940929	CA 94-2157376	19940314
	AU 9464264	A1	19941011	AU 94-64264	19940314
	AU 685443	B2	19980122		
	BR 9405957	A	19951212	BR 94-5957	19940314
	EP 689454	A1	19960103	EP 94-911894	19940314
	EP 689454	B1	19970910		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	CN 1119829	A	19960403	CN 94-191582	19940314
	HU 72916	A2	19960628	HU 95-1979	19940314
	JP 08508722	T2	19960917	JP 94-520640	19940314
	AT 157882	E	19970915	AT 94-911894	19940314
	EP 812593	A1	19971217	EP 97-101617	19940314
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, MC, PT, IE, SI, FI				
	ES 2109685	T3	19980116	ES 94-911894	19940314
	ZA 9401957	A	19950131	ZA 94-1957	19940321
	IL 109056	A1	19980615	IL 94-109056	19940321
	NO 9503759	A	19950922	NO 95-3759	19950922
	FI 9504514	A	19950922	FI 95-4514	19950922

Searcher : Shears 308-4994

09/210995

US 5776468            A     19980707            US 96-525638        19960212  
AU 9675416            A1    19970213            AU 96-75416        19961218  
PRAI GB 93-6029        19930323  
GB 94-3417            19940223  
EP 94-911894        19940314  
WO 94-EP818          19940314  
AB Novel vaccine compns. contg. small (<120-nm) particles of  
3-O-deacylated monophosphoryl lipid A (I) are provided which have  
superior immunol. properties. When formulated with Al(OH)<sub>3</sub>, I interacts with Al(OH)<sub>3</sub> and the  
antigen to form a single entity. Thus, 1-20 .mu.g hepatitis B  
surface antigen was adsorbed onto 30-100 .mu.g Al(OH)<sub>3</sub> in phosphate buffer, and 30-50 .mu.g of a sonicated  
suspension of I was added (final vol. 600 .mu.L). Maturation of the  
compn. occurred during storage at 4.degree..  
IT 21645-51-2, Aluminum hydroxide,  
biological studies  
RL: BAC (Biological activity or effector, except adverse); THU  
(Therapeutic use); BIOL (Biological study); USES (Uses)  
(vaccine compns. contg. 3-O-deacylated monophosphoryl lipid A and  
adjuvant)

L11 ANSWER 9 OF 16 CAPLUS COPYRIGHT 1999 ACS  
AN 1994:62253 CAPLUS  
DN 120:62253  
TI Combined vaccines comprising hepatitis B surface antigen and other  
antigens  
IN Petre, Jean; Hauser, Pierre  
PA Smithkline Beecham Biologicals (S.A.), Belg.  
SO PCT Int. Appl., 30 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9324148	A1	19931209	WO 93-EP1276	19930515
	W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9343156	A1	19931230	AU 93-43156	19930515
	EP 642355	A1	19950315	EP 93-912750	19930515
	EP 642355	B1	19980715		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 07508267	T2	19950914	JP 93-500162	19930515
	HU 71791	A2	19960228	HU 94-3366	19930515

Searcher : Shears 308-4994

09/210995

EP 835663            A2    19980415            EP 97-204034            19930515  
EP 835663            A3    19990303  
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC,  
PT, IE

PL 174077	B1	19980630	PL 93-306304	19930515
CZ 283910	B6	19980715	CZ 94-2892	19930515
AT 168271	E	19980815	AT 93-912750	19930515
ES 2118963	T3	19981001	ES 93-912750	19930515
ZA 9303541	A	19940621	ZA 93-3541	19930521
IL 105770	A1	19980816	IL 93-105770	19930521
CN 1085450	A	19940420	CN 93-107319	19930522
NO 9404475	A	19950118	NO 94-4475	19941122
FI 9405483	A	19950120	FI 94-5483	19941122
AU 9716480	A1	19970529	AU 97-16480	19970324

PRAI GB 92-11081            19920523  
GB 92-13308            19920623  
EP 93-912750            19930515  
WO 93-EP1276            19930515

AB Stable and effective multivalent vaccine compns. comprising  
Hepatitis B surface antigen (HBsAg) are described wherein the HBsAg  
component is stable for 1 wk at 37.degree. and is highly immunogenic  
when is administered to infants. The compns. typically comprise  
HBsAg adsorbed to **Al phosphate (I)** and other  
antigens, esp. those suitable for use in a pediatrics, adsorbed to I  
or **Al(OH)3 (II)**. A conc. contg. 25,000 Lf of  
diphtheria toxoid and 10,000 Lf of tetanus toxoid absorbed to 0.35 g  
of II was prepd. in a final vol. of 0.15 L of isotonic saline and  
was adjusted to pH=6-7. The conc. was combined with 0.05 L of HBsAg  
adsorbed to I in isotonic saline and the mixt. brought to 0.5L with  
isotonic saline. A dose of 0.5 mL vaccine contained diphtheria  
toxoid 25Lf, tetanus toxoid 10Lf, and HBsAg 10.mu.g protein.

IT 21645-51-2, **Aluminum hydroxide**,  
biological studies

RL: BIOL (Biological study)  
(antigens adsorbed on, multivalent vaccine contg. hepatitis B  
surface antigen and)

IT 7784-30-7, **Aluminum phosphate**

RL: BIOL (Biological study)  
(hepatitis B surface antigen adsorbed on, multivalent vaccine  
contg. antigens and)

L11 ANSWER 10 OF 16 CAPLUS COPYRIGHT 1999 ACS

AN 1993:678730 CAPLUS

DN 119:278730

TI Hepatitis vaccines containing 3-O-deacylated monophosphoryl lipid A

IN Garcon-Johnson, Nathalie Marie Josephe; Hauser, Pierre; Thiriart,  
Clothilde; Voet, Pierre

PA SmithKline Beckman Corp., Belg.

SO PCT Int. Appl., 32 pp.

Searcher : Shears 308-4994



09/210995

CODEN: PIXXD2

DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9319780	A1	19931014	WO 93-EP712	19930324
	W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9337516	A1	19931108	AU 93-37516	19930324
	EP 633784	A1	19950118	EP 93-906601	19930324
	EP 633784	B1	19961227		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 07505372	T2	19950615	JP 93-517046	19930324
	HU 69931	A2	19950928	HU 94-2758	19930324
	AT 146678	E	19970115	AT 93-906601	19930324
	ES 2098029	T3	19970416	ES 93-906601	19930324
	CZ 283424	B6	19980415	CZ 94-2355	19930324
	IL 105161	A1	19980816	IL 93-105161	19930325
	CN 1085805	A	19940427	CN 93-105232	19930326
	FI 9404442	A	19940926	FI 94-4442	19940926
	NO 9403571	A	19941114	NO 94-3571	19940926
	AU 9664457	A1	19961107	AU 96-64457	19960905
PRAI	GB 92-6786		19920327		
	GB 92-6788		19920327		
	GB 92-6789		19920327		
	GB 92-6797		19920327		
	WO 93-EP712		19930324		
AB	A vaccine formulation for the treatment or prophylaxis of hepatitis, esp. hepatitis B (HB) infection, comprises a hepatitis antigen and a carrier such as alum in combination with 3-O-deacylated monophosphoryl lipid A (I). Thus, 1-20.mu.g of hepatitis B surface antigen in phosphate buffer soln. (1mg/mL) was absorbed on 30-100.mu.g of Al(OH)3 and the soln. was then added to 30-50.mu.g of I (1mg/mL). Vol. was adjusted to 600.mu.L for providing 10 injecting doses for mice. Immunization of mice with above vaccine improved the kinetics of anti-HB response and more anti-HB antibodies was produced as compared to controls with no I.				
IT	21645-51-2, Aluminum hydroxide, biological studies RL: BIOL (Biological study) (vaccine contg. hepatitis antigens and deacylated monophosphoryl lipid A and)				

Searcher : Shears 308-4994

09/210995

L11 ANSWER 11 OF 16 CAPLUS COPYRIGHT 1999 ACS  
AN 1993:480195 CAPLUS  
DN 119:80195  
TI Protein-dimeric polysaccharide conjugate vaccine  
IN Marburg, Stephen; Tolman, Richard L.  
PA Merck and Co., Inc., USA  
SO Eur. Pat. Appl., 29 pp.  
CODEN: EPXXDW  
DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 534764	A1	19930331	EP 92-308730	19920924
	R: CH, DE, FR, GB, IT, LI, NL				
	US 5371197	A	19941206	US 91-766242	19910924
	CA 2078359	AA	19930325	CA 92-2078359	19920916
	JP 05279399	A2	19931026	JP 92-254695	19920924
PRAI	US 91-766242		19910924		

AB A conjugate immunogen having polysaccharide moieties derived from bacterial sources, provides a multivalent vaccine with a low protein to polysaccharide ratio. The vaccine reduces complications assocd. with injection of protein immunogens due to pyrogenic responses, such as swelling and pain, and is particularly suitable for administration to infants. OmpC protein conjugates with polyribosyl-ribitol-phosphate (PRP) was reacted with Streptococcus pneumoniae 6A polysaccharide (PnPs6A) to obtain a gelatinous mixt., which was filtered and washed. PnPs6A-PRP-OmpC conjugate was adsorbed onto Al(OH)<sub>3</sub>, then was i.m. administered to chinchillas at the dose of 0.08.mu.g PnPs6A and 0.12.mu.g PRP at 0 and 4 wks and animals were bled at 0, 2, 4, 6, and 8 wks. There were high titers of both anti-PnPs6A and anti-PRP antibody.

L11 ANSWER 12 OF 16 CAPLUS COPYRIGHT 1999 ACS  
AN 1992:405648 CAPLUS  
DN 117:5648  
TI Augmentation by interleukins of the antibody response to a conjugate vaccine against *Haemophilus influenzae* b  
AU Bixler, Garvin S., Jr.; Pillai, Subramonia  
CS Praxis Biol., Inc., Rochester, NY, 14623, USA  
SO Adv. Exp. Med. Biol. (1991), 303(Immunobiol. Proteins Pept. 6), 185-90  
CODEN: AEMBAP; ISSN: 0065-2598  
DT Journal  
LA English  
AB Interleukins (ILs) have been recognized as potential adjuvants for use during vaccination. The immunogenicity of some poorly immunogenic bacterial capsular polysaccharides have been improved by

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conjugation to a protein carrier. Augmentation of the immune response to these glycoconjugates, however, may be realized in the presence of ILs. The antibody response to one such vaccine which comprises a oligosaccharide derived from the capsule of *H. influenzae* type b coupled to CRM197 (HbOC) can be augmented in this manner. A suboptimal dose (0.1 .mu.g) of HbOC and varying concns. of IL-1.alpha. or IL-1.beta. (102-5 .times. 105 U) were injected i.m. at 0 and 2 wks into Swiss Webster mice. Vaccines were also formulated with and without **aluminum phosphate**. Antibody to the oligosaccharide was detd. by Farr assay. In 3/3 expts., IL-1.alpha. enhanced primary and secondary antibody responses whereas with IL-1.beta., only a slight increase in the primary antibody response was seen but enhanced secondary responses were obsd. Thus, IL-1.alpha. and to some extent IL-1.beta. enhanced the primary and secondary antibody responses to a glycoconjugate vaccine.

L11 ANSWER 13 OF 16 CAPLUS COPYRIGHT 1999 ACS

AN 1991:427277 CAPLUS

DN 115:27277

TI A semi-synthetic vaccine involving CRM 197 as carrier for *H. influenzae* type B capsular oligosaccharides

AU Costantino, P.; Giannozzi, A.; Podda, A.; Viti, S.

CS Sclavo S.p.A., Siena, Italy

SO Zentralbl. Bakteriол., Suppl. (1990), 19(Bact. Protein Toxins), 527-8

CODEN: ZBASE2

DT Journal

LA English

AB Glycoconjugates between CRM 197 (a nontoxic deriv. of diphtheria toxin) and *Haemophilus influenzae* type B (Hib) capsular polysaccharide (3 .mu.g of oligosaccharide linked to 45 .mu.g of CRM 197 and adsorbed on 1 mg **Al(OH)3**) used as a single dose in adult volunteers elicited an increase in anti-Hib and antidiphtheria toxin antibodies and none of the humans showed adverse reactions to the product.

L11 ANSWER 14 OF 16 CAPLUS COPYRIGHT 1999 ACS

AN 1988:73342 CAPLUS

DN 108:73342

TI Synergistic effect of detergents and **aluminum phosphate** on the humoral immune response to bacterial and viral membrane proteins

AU Teerlink, Tom; Beuvery, E. Coen; Evenberg, Dolf; Van Wezel, Toon L.

CS Dep. Bact. Vaccines, Natl. Inst. Public Health Environ. Hyg. (RIVM), Bilthoven, 3720 BA, Neth.

SO Vaccine (1987), 5(4), 307-14

CODEN: VACCDE; ISSN: 0264-410X

DT Journal

Searcher : Shears 308-4994

LA English

AB The influence of detergents on the immunogenic activity of the major outer membrane protein of *Neisseria gonorrhoeae* was investigated. Most detergents tested enhanced the immune response. This effect was synergistic with the adjuvant activity of AlPO<sub>4</sub>. The combination of detergent and AlPO<sub>4</sub> showed a stronger adjuvant activity than Freund's complete adjuvant. The adjuvant effect was only obsd. with protein preps. with very low lipopolysaccharide content. The immunostimulating effect of detergents was also obsd. with meningococcal group C polysaccharide conjugated to a *Haemophilus influenzae* type b outer membrane protein and with the fusion protein of measles virus. The influence of some detergent parameters (crit. micelle concn., hydrophile-lipophile balance, and charge) was investigated.

IT 7784-30-7, Aluminum phosphate

RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(immune adjuvant activity of, detergents synergism with, in response to bacterial and viral membrane proteins)

L11 ANSWER 15 OF 16 CAPLUS COPYRIGHT 1999 ACS

AN 1986:223162 CAPLUS

DN 104:223162

TI Quantitative and qualitative analyses of serum antibodies elicited in adults by *Haemophilus influenzae* type b and pneumococcus type 6A capsular polysaccharide-tetanus toxoid conjugates

AU Schneerson, Rachel; Robbins, John B.; Parke, James C., Jr.; Bell, Clara; Schlesselman, James J.; Sutton, Ann; Wang, Zhen; Schiffman, Gerald; Karpas, Arthur; Shiloach, Joseph

CS Lab. Dev. Mol. Immunity, Natl. Inst. Child Health Human Dev., Bethesda, MD, 20892, USA

SO Infect. Immun. (1986), 52(2), 519-28

CODEN: INFIBR; ISSN: 0019-9567

DT Journal

LA English

AB Covalent binding to immunogenic proteins increases the immunogenicity of the capsular polysaccharides of *Haemophilus influenzae* type b (Hib) and pneumococcus type 6A (Pn6A). Conjugates composed of Hib, Pn6A, or the cross-reacting *Escherichia coli* K100 covalently bound to tetanus toxoid (TT) were injected into young adult volunteers. Local reactions were common and were probably due to Arthus reactivity mediated by the preexisting antibodies reacting with the TT component of the conjugates. Fever occurred in .apprx.10% of the volunteers after the 1st injection; no volunteers had fever after the 2nd injection. Similar levels of Hib or Pn6A antibodies were elicited by either 50- or 100-.mu.g doses or by concurrent injection of 2 different conjugates (Hib-TT and Pn6A-TT or Hib-TT and

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K100-TT). The Hib-TT elicited about a 180-fold increase in Hib antibodies, and the Pn6A-TT conjugate elicited about an 8-fold increase in Pn6A antibodies after 1 injection. Booster reactions were not elicited in adults; similar levels of antibodies in the 5 exptl. groups suggested that the responses elicited by the conjugates were maximal. A 1-way cross-reaction was noted as Pn6A conjugates elicited rises of Hib antibodies in 13 of 20 volunteers; only 4 of 59 volunteers immunized with Hib-TT had increases in Pn6A antibodies. The preimmunization Hib antibodies were composed of IgM, IgA, and IgG. The postimmunization sera showed an increase in all 3 isotypes; the elevation of the IgG was the highest of the 3 isotypes. Conjugate-induced antibodies to both the polysaccharide and TT-exerted biol. activities that have been correlated with immunity. Adsorption of the Hib-TT onto Al hydroxide resulted in higher levels and an earlier Hib antibody response in infant rhesus. These results encourage the evaluation of Hib and Pn6A conjugates in human children and infants.

L11 ANSWER 16 OF 16 CAPLUS COPYRIGHT 1999 ACS  
 AN 1985:539889 CAPLUS  
 DN 103:139889  
 TI Enhancement of immunogenic activity of ribosomal preparations from *Haemophilus influenzae* by various adjuvants  
 AU Cabrera-Contreras, R.; Plescia, O.; Solotorovsky, M.; Lynn, M.  
 CS Waksman Inst. Microbiol., Rutgers Univ., New Brunswick, NJ, 08903, USA  
 SO Vaccine (1985), 3(2), 103-8  
 CODEN: VACCDE  
 DT Journal  
 LA English  
 AB Ribosomes from *H. influenzae* type b have been reported to have immunoprotective activity in animals whos immunity can be enhanced by adjuvants. In this report the adjuvant activity was evaluated from several compds. in conjunction with ribosomes from the b and c serotypes of *H. influenzae*. Alhydrogel, saponin and diphtheria-pertussis-tetanus vaccine were found to significantly enhance the immunoprotective response in mice, equally or exceeding the activity of Freund's incomplete adjuvant. All of these adjuvants also enhanced significantly the IgM response of mice to sheep red blood cells. Ribosomes also enhanced this response. Among the compds. failing to provide adjuvant activity for ribosomes were poly(A:U), muramyl dipeptide, mycobacterial ext., dimethylglycine, methylated bovine serum albumin, sodium diethylthiocarbamate, and cetyltrimethylammonium bromide.  
 IT 21645-51-2, biological studies  
 RL: BIOL (Biological study)  
 (immunogenicity of *Haemophilus influenzae* ribosome enhancement by)

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09/210995

(FILE 'MEDLINE, BIOSIS, EMBASE, LIFESCI, BIOTECHDS, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, PROMT, TOXLIT, TOXLINE, DRUGU, DRUGNL, DRUGB, DRUGLAUNCH' ENTERED AT 12:50:06 ON 25 MAR 1999)

L12 107 SEA ABB=ON PLU=ON L10  
L13 105 SEA ABB=ON PLU=ON L12 NOT L7  
L14 80 DUP REM L13 (25 DUPLICATES REMOVED)  
L15 55 SEA ABB=ON PLU=ON L14 AND (ADJUVANT OR IMMUNIS? OR  
IMMUNIZ? OR VACCIN? OR IMMUNOGEN?)  
L16 16 SEA ABB=ON PLU=ON L15 AND ADMIN?

L16 ANSWER 1 OF 16 MEDLINE

AN 97270468 MEDLINE

DN 97270468

TI MF59 adjuvant enhances antibody responses of infant  
baboons immunized with *Haemophilus*  
*influenzae* type b and *Neisseria meningitidis* group C  
oligosaccharide-CRM197 conjugate vaccine.

AU Granoff D M; McHugh Y E; Raff H V; Mokatrin A S; Van Nest G A  
CS Chiron Vaccines, Emeryville, California 94608, USA..

danvgranoff@cc.chiron.com

SO INFECTION AND IMMUNITY, (1997 May) 65 (5) 1710-5.  
Journal code: GO7. ISSN: 0019-9567.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Cancer Journals; Priority Journals

EM 199707

AB The ability of the adjuvant MF59 to enhance the  
immunogenicity of polysaccharide-protein conjugate  
vaccines was investigated in infant baboons. MF59 consists  
of stable droplets (<250 nm) of the metabolizable oil squalene and  
two surfactants, polyoxyethylene sorbitan monooleate and sorbitan  
trioleate, in an oil-in-water emulsion. In humans, MF59 is well  
tolerated and enhances the immunogenicity of recombinant  
protein subunit or particle vaccines. Its effect on the  
immunogenicity of polysaccharide-protein conjugate  
vaccines is unknown. Baboons 1 to 4 months of age were  
immunized intramuscularly with *Neisseria meningitidis* group  
C and *Haemophilus influenzae* type b (Hib)  
oligosaccharide-CRM197 conjugate vaccines. The lyophilized  
vaccines were reconstituted with phosphate-buffered saline  
(PBS), Al(OH)<sub>3</sub> (alum), or MF59. Groups of five  
animals each were given three injections of the respective  
formulations, with one injection every 4 weeks. Four weeks after  
each immunization, the MF59 group had up to 7-fold-higher  
geometric mean anticapsular-antibody titers than the alum group and  
5- to 10-fold-higher *N. meningitidis* group C bactericidal-antibody  
titers. Twenty-one weeks after the third immunization, the

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MF59 group still showed 5- to 10-fold-higher anticapsular-antibody titers. The antibody responses of the animals given the vaccines reconstituted with PBS were low at all times measured. Both the MF59 and alum groups, but not the PBS group, showed booster antibody responses to unconjugated Hib and N. meningitidis group C polysaccharides, results consistent with induction of memory B cells. Thus, MF59 may be useful for accelerating and augmenting immunity to polysaccharide-protein conjugate vaccines in infants.

L16 ANSWER 2 OF 16 MEDLINE

AN 92214276 MEDLINE

DN 92214276

TI Augmentation by interleukins of the antibody response to a conjugate vaccine against *Haemophilus influenzae* b.

AU Bixler G S Jr; Pillai S

CS Praxis Biologics, Inc., Rochester, New York 14623..

SO ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1991) 303 185-90.  
Journal code: 2LU. ISSN: 0065-2598.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199207

AB Interleukins have been recognized as potential adjuvants for use during vaccination. The immunogenicity of some poorly immunogenic bacterial capsular polysaccharides have been improved by conjugation to a protein carrier. Augmentation of the immune response to these glycoconjugates, however, may be realized in the presence of interleukins. The antibody response to one such vaccine which comprises a oligosaccharide derived from the capsule of *Haemophilus influenzae* type b coupled to CRM197 (HbOC) can be augmented in this manner. A suboptimal dose (0.1 microgram) of HbOC and varying concentrations of IL-1 alpha or IL-1 beta (10(2) - 5 x 10(5) U) were injected intramuscularly at 0 and 2 weeks into Swiss Webster mice. Vaccines were also formulated with and without aluminum phosphate. Antibody to the oligosaccharide was determined by Farr assay. In 3/3 experiments, IL-1 alpha enhanced primary and secondary antibody responses whereas with IL-1 beta, only a slight increase in the primary antibody response was seen but enhanced secondary responses were observed. Thus, IL-1 alpha and to some extent IL-1 beta enhanced the primary and secondary antibody responses to a glycoconjugate vaccine.

L16 ANSWER 3 OF 16 MEDLINE

AN 90271024 MEDLINE

Searcher : Shears 308-4994

DN 90271024  
 TI Duration of serum antibodies elicited by *Haemophilus influenzae* type b capsular polysaccharide alone or conjugated to tetanus toxoid in 18- to 23-month-old children.  
 AU Claesson B A; Schneerson R; Trollfors B; Lagergard T; Taranger J; Robbins J B  
 CS Department of Infectious Diseases, University of Goteborg, Sweden..  
 SO JOURNAL OF PEDIATRICS, (1990 Jun) 116 (6) 929-31.  
 Journal code: JLZ. ISSN: 0022-3476.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals  
 EM 199009

L16 ANSWER 4 OF 16 MEDLINE  
 AN 86283798 MEDLINE  
 DN 86283798  
 TI Immunogenicity in infants of *Haemophilus influenzae* type B polysaccharide in a conjugate vaccine with *Neisseria meningitidis* outer-membrane protein.  
 AU Einhorn M S; Weinberg G A; Anderson E L; Granoff P D; Granoff D M  
 NC RO1 AI 17962 (NIAID)  
 T32 AI 07172 (NIAID)  
 RR-36 (NCRR)  
 SO LANCET, (1986 Aug 9) 2 (8502) 299-302.  
 Journal code: LOS. ISSN: 0140-6736.  
 CY ENGLAND: United Kingdom  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals  
 EM 198611  
 AB 63 children, aged 2-17 months, were given a new conjugate vaccine composed of the capsular polysaccharide of *Haemophilus influenzae* type b linked to a *Neisseria meningitidis* outer-membrane protein. Subjects under 7 months received two injections separated by 1 month, and older subjects received either one or two injections. There were no systemic reactions to this vaccine when it was given with aluminium hydroxide. A single injection of vaccine was highly immunogenic; the geometric mean serum anticapsular antibody concentrations before immunisation and 1 month later were 0.35 microgram/ml and 0.98 microgram/ml for babies of 2-3 months, 0.12 microgram/ml and 1.85 micrograms/ml for those of 4-6 months, and 0.15 microgram/ml and 4.1 micrograms/ml for those of 8-17 months (p less than or equal to 0.003 for each age group). After a second injection of vaccine, 80% and 76% of infants of 2-3 and 4-6 months, respectively, had antibody concentrations greater than 1.0

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micrograms/ml. Most subjects showed evidence of IgG responses as measured by enzyme-linked immunosorbent assay. 6-12 months after immunisation, serum antibody levels had fallen (p less than 0.05) but they remained higher than those of unimmunized controls (p less than 0.001).

L16 ANSWER 5 OF 16 MEDLINE

AN 86194736 MEDLINE

DN 86194736

TI Quantitative and qualitative analyses of serum antibodies elicited in adults by *Haemophilus influenzae* type b and pneumococcus type 6A capsular polysaccharide-tetanus toxoid conjugates.

AU Schneerson R; Robbins J B; Parke J C Jr; Bell C; Schlesselman J J; Sutton A; Wang Z; Schiffman G; Karpas A; Shiloach J

SO INFECTION AND IMMUNITY, (1986 May) 52 (2) 519-28.  
Journal code: G07. ISSN: 0019-9567.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 198608

AB Covalent binding to immunogenic proteins increases the immunogenicity of the capsular polysaccharides of *Haemophilus influenzae* type b (Hib) and pneumococcus type 6A (Pn6A). Conjugates composed of Hib, Pn6A, or the cross-reacting *Escherichia coli* K100 covalently bound to tetanus toxoid (TT) were injected into young adult volunteers. Local reactions were common and were probably due to Arthus reactivity mediated by the preexisting antibodies reacting with the TT component of the conjugates. Fever occurred in about 10% of the volunteers after the first injection; no volunteers had fever after the second injection. Similar levels of Hib or Pn6A antibodies were elicited by either 50- or 100-micrograms doses or by concurrent injection of two different conjugates (Hib-TT and Pn6A-TT or Hib-TT and K100-TT). The Hib-TT elicited about a 180-fold increase in Hib antibodies, and the Pn6A-TT conjugate elicited about an 8-fold increase in Pn6A antibodies after one injection. Booster reactions were not elicited in adults; similar levels of antibodies in the five experimental groups suggested that the responses elicited by the conjugates were maximal. A one-way cross-reaction was noted as Pn6A conjugates elicited rises of Hib antibodies in 13 of 20 volunteers; only 4 of 59 volunteers immunized with Hib-TT had increases in Pn6A antibodies. The preimmunization Hib antibodies were composed of immunoglobulin M (IgM), IgA, and IgG. The postimmunization sera showed an increase in all three isotypes; the elevation of the IgG was the highest of the three isotypes. Conjugate-induced antibodies to both the polysaccharide and TT exerted biological activities that have been correlated with

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immunity. Adsorption of the Hib-TT onto aluminium hydroxide resulted in higher levels and an earlier Hib antibody response in infant rhesus. These results encourage the evaluation of Hib and Pn6A conjugates in human children and infants.

L16 ANSWER 6 OF 16 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.  
AN 97345547 EMBASE  
DN 1997345547  
TI Fatal hyperphosphatemia after oral phosphate overdose in a premature infant.  
AU Perlman J.M.  
CS Prof. J.M. Perlman, Department of Pediatrics, Texas Univ. Southwestern Med. Ctr., 5323 Harry Hines Boulevard, Dallas, TX 75235-9063, United States. jperlman@mednet.swmed.edu  
SO American Journal of Health-System Pharmacy, (1997) 54/21 (2488-2490).  
Refs: 11  
ISSN: 1079-2082 CODEN: AHSPEK  
CY United States  
DT Journal; Article  
FS 007 Pediatrics and Pediatric Surgery  
037 Drug Literature Index  
052 Toxicology  
LA English

L16 ANSWER 7 OF 16 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.  
AN 93042540 EMBASE  
DN 1993042540  
TI Vaccine development: Progression from target antigen to product.  
AU Ellis R.W.  
CS Cellular and Molecular Biology, Merck Sharp and Dohme Research Lab., West Point, PA 19486, United States  
SO Advances in Experimental Medicine and Biology, (1992) 327/- (263-271).  
CODEN: AEMBAP  
CY United States  
DT Journal; Conference Article  
FS 004 Microbiology  
007 Pediatrics and Pediatric Surgery  
017 Public Health, Social Medicine and Epidemiology  
026 Immunology, Serology and Transplantation  
037 Drug Literature Index  
LA English

L16 ANSWER 8 OF 16 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD  
AN 94-145667 [18] WPIDS  
DNC C94-066614  
TI Combined paediatric vaccine compsn. - comprising a mixt.  
Searcher : Shears 308-4994

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of diphtheria, tetanus, pertussis and *Haemophilus influenzae* type b antigens.

DC B04 D16  
IN HACKELL, J G; HOGERMAN, D A; MADORE, D V; PARADISO, P R  
PA (AMCY) AMERICAN CYANAMID CO  
CYC 27  
PI EP 594950 A1 940504 (9418)\* EN 10 pp  
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE  
NO 9303856 A 940428 (9424)  
AU 9350290 A 940512 (9425)  
FI 9304725 A 940428 (9426)  
CA 2109159 A 940428 (9428)  
CZ 9302272 A3 940518 (9428)  
NZ 250029 A 940927 (9438)  
HU 67239 T 950328 (9518)  
TW 256774 A 950911 (9547)  
JP 07300427 A 951114 (9603) 1 pp  
AU 669570 B 960613 (9631)  
IL 107387 A 970415 (9726)  
CZ 283587 B6 980513 (9825)  
SG 47725 A1 980417 (9827)  
EP 594950 B1 990127 (9909) EN  
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE  
ADT EP 594950 A1 EP 93-111735 930722; NO 9303856 A NO 93-3856 931026; AU  
9350290 A AU 93-50290 931026; FI 9304725 A FI 93-4725 931026; CA  
2109159 A CA 93-2109159 931025; CZ 9302272 A3 CZ 93-2272 931026; NZ  
250029 A NZ 93-250029 931022; HU 67239 T HU 93-3028 931026; TW  
256774 A TW 93-106371 930810; JP 07300427 A JP 93-285570 931021; AU  
669570 B AU 93-50290 931026; IL 107387 A IL 93-107387 931025; CZ  
283587 B6 CZ 93-2272 931026; SG 47725 A1 SG 96-4072 930722; EP  
594950 B1 EP 93-111735 930722  
FDT AU 669570 B Previous Publ. AU 9350290; CZ 283587 B6 Previous Publ.  
CZ 9302272  
PRAI US 92-966995 921027  
AN 94-145667 [18] WPIDS  
AB EP 594950 A UPAB: 960129

Combined paediatric vaccine compsn. comprising, in a single immunising dose, a mixt. of (i) diphtheria, tetanus and pertussis antigens and (ii) a conjugate of fragments of the capsular polysaccharide antigen of *Haemophilus influenzae* type b and CRM197 protein, in an aq. vehicle. The combine vaccine compsn. provides enhanced antibody response, by infants, to each of the diphtheria, tetanus, pertussis and *Haemophilus influenzae* type b vaccine components.

The diphtheria, antigen is diphtheria toxoid (esp. adsorbed on aluminium phosphate), the tetanus antigen is tetanus toxoid (esp. adsorbed on aluminium phosphate), and the pertussis antigen is inactive Bordetella

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pertussis cells (esp. suspended in a soln. contg. potassium phosphate monobasic, sodium phosphate dibasic and sodium chloride). Admin. is esp. intramuscular.

ADVANTAGE - The combination vaccine exhibits improved immunogenicity in infants for each of the four vaccine components when compared to DTP and Haemophilus influenzae type b conjugate vaccines administered concurrently but separately. The vaccines are safe to use.

Dwg.0/0

Dwg.0/0

- L16 ANSWER 9 OF 16 SCISEARCH COPYRIGHT 1999-ISI (R) - - - - -
- AN 1998:235986 SCISEARCH
- GA The Genuine Article (R) Number: BK54S
- TI Biodegradable polymer microspheres as vaccine adjuvants and delivery systems
- AU Gupta R K (Reprint); Chang A C; Siber G R
- CS WYETH LEDERLE VACCINES & PEDIAT, 401 N MIDDLETOWN RD, PEARL RIVER, NY 10965 (Reprint)
- CYA USA
- SO DEVELOPMENTS IN BIOLOGICAL STANDARDIZATION, (MAR 1998) Vol. 92, pp. 63-78.  
 Publisher: KARGER, POSTFACH, CH-4009 BASEL, SWITZERLAND.  
 ISSN: 0301-5149.
- DT Article; Journal
- FS LIFE
- LA English
- REC Reference Count: 83
- \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*
- AB Though vaccination has been the most cost-effective way of controlling infectious diseases, the logistics of delivering at least two to three doses of conventional vaccines for primary immunization to achieve protection are difficult and compliance is frequently inadequate, particularly in developing countries. In recent years biodegradable polymer microspheres have received much attention for the purposes of controlled release of antigens, (i) to reduce the number of doses needed for primary immunization to as few as a single dose and (ii) to target an antigen to microfold cells on mucosal surfaces after oral administration or to antigen-presenting cells after parenteral inoculations. A variety of vaccine antigens have been encapsulated in microspheres usually composed of poly (lactic/glycolic) acid (PLGA). Based on the size of the microspheres, molecular weight of polymer and ratio of lactic to glycolic acid in the polymer, the antigen may be targeted to various cells of the immune system or it may form a depot at the site of injection, allowing the slow release of the antigen for extended periods. Additionally, another adjuvant may be
- Searcher : Shears 308-4994

incorporated inside microspheres together with the antigen, further enhancing or modulating the immune response to the desired type. The major problems in developing controlled-release vaccines include instability of vaccine antigens during micro-encapsulation, storage and subsequent hydration. We encapsulated tetanus toroid (TT) and *Haemophilus influenzae* type b capsular polysaccharide conjugated to TT (Hib-T) inside PLGA microspheres and evaluated the antibody levels in mice. A single injection of these micro-encapsulated vaccines elicited high antibody levels which persisted for several months. The antibody levels were similar or superior to those elicited by conventional formulations of AlPO<sub>4</sub>-adsorbed TT or soluble Hib-T conjugate vaccine.

L16 ANSWER 10 OF 16 PROMT COPYRIGHT 1999 IAC

AN 1998:284484 PROMT

TI Conference Coverage (ECPI Combination Vaccines) Many Hurdles for Successful Combination Vaccines

SO Vaccine Weekly, (8 Jun 1998) pp. N/A.

ISSN: 1074-2921.

LA English

WC 1182

\*FULL TEXT IS AVAILABLE IN THE ALL FORMAT\*

AB It's more than just mixing.

Combinations of existing vaccines are more than the sum of their parts: they are complex new vaccine entities. Developers wishing to take advantage of the trend toward combination vaccines must make similarly complex plans, and must do so early in the course of combination vaccine development.

"There are significant challenges to the development and implementation of combination vaccines," warned Ronald Ellis, senior director of vaccine research and development for Astra Research Center, Boston, Massachusetts. "An integrated development plan should be established early in the program." Ellis discussed strategies for making such plans in an address to the European Center for Pharmaceutical Information (ECPI) Rapid Development of Combination Vaccines Conference, held April 20-22, 1998, in London, England.

After facing the technical challenges of creating a combination vaccine and the clinical challenges of proving its efficacy, it would seem that the job would be done. But equally formidable regulatory, manufacturing, and marketing challenges still remain.

"All these issues must be planned to have a successful vaccine in the end," Ellis said.

One the most important technical challenges to combination vaccines stems from the fact that many component vaccines are formulated with aluminum salts as adjuvants. But different vaccines may use

Searcher : Shears 308-4994

aluminum hydroxide, aluminum hydroxyphosphate, or aluminum phosphate.

"Aluminum-adsorbed antigens may encounter and exchange onto the 'new' aluminum," Ellis observed. "And non-adsorbed antigens may bind to aluminum."

Such interactions, difficult to foresee, may significantly affect the immunogenicity of component vaccines.

Other physical interactions that may cause problems are those with excipients, or additives, used to stabilize component vaccines. These chemicals may have unexpected effects on other vaccine antigens.

Moreover, the different vaccines may themselves interact in ways that discourage proper use: by causing clumping, aggregation, discoloration, or by needing vigorous mixing. Sometimes an ingenious solution is required. Ellis pointed to the example of the combined diphtheria-tetanus-whole-cell pertussis (DTPw) and intravenous polio vaccine (IPV). DTPw is preserved with thimerosal, which over time destroys IPV and thus makes it impossible to store the combined vaccines.

THIS IS AN EXCERPT: COPYRIGHT 1998 Charles W Henderson

L16 ANSWER 11 OF 16 PROMT COPYRIGHT 1999 IAC

AN 1998:274239 PROMT

TI Primer on vaccinations

Lengthy article of an introductory nature

AU Sindelar, Robert D.

SO Drug Topics, (18 May 1998) pp. 81.

ISSN: 0012-6616.

LA English

WC 5375

\*FULL TEXT IS AVAILABLE IN THE ALL FORMAT\*

AB INTRODUCTION

Vaccinations are among the most cost-effective and widely used public health interventions. Yet public concerns focus on the health risks associated with vaccines as much as on the reduction in incidence of vaccine-preventable diseases. Pharmacists can play an important role as vaccination leaders in immunization advocacy, in patient and health-care education, and in the role of immunizers. As pharmacists develop these expanding roles, a review of the principles of vaccination may prove useful. While this article can provide only the basics, the reader is encouraged to use it as a foundation for further studies.

The immune response. The human immune system is a complex regulatory and surveillance system composed of interacting immune cells, various tissues, mediators, and immunoglobulins (antibody molecules). Host-protective in nature, the immune system inactivates invading microorganisms, detects and rejects tumors, neutralizes

Searcher : Shears 308-4994

toxins, and performs other host-defense functions. **Immunogens** are substances that can evoke an immune response with the production of immunoglobulins; an **immunogen** that can itself combine with an immune response-generated immunoglobulin is an antigen. In simplest terms, the immune system cells fall into two general categories that interact with each other: lymphocytes (T-lymphocytes or T-cells and B-lymphocytes or B-cells) that recognize antigens (in effect, **immunization**) on the surface of invading pathogens and cancer cells; and phagocytes, cells that internalize pathogens and degrade them.

There is a very important difference between the two categories: The response of specific (adaptive) immunity, involving the B- and T-lymphocytes, improves with each successive exposure to the same antigen. This "immunological memory" results from the clonal selection of genetically specific B- and T-lymphocytes (memory cells). The response of nonspecific (innate) immunity, involving phagocytic cells, physical/chemical barriers, and the complement cascade does not change upon repeated exposure to a given antigen. Specific immunity may be further divided into humoral immunity (immunity attributable to B-lymphocytes and immunoglobulins) and cellular immunity (mediated by specifically sensitized T-lymphocytes).

THIS IS AN EXCERPT: COPYRIGHT 1998 Medical Economics Publishing

L16 ANSWER 12 OF 16 PROMT COPYRIGHT 1999 IAC

AN 96:518038 PROMT

TI Merck & Co. Inc.: Comvax (Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine)

SO PR Newswire, (4 Oct 1996) pp. 1004NYF012.

LA English

WC 5155

\*FULL TEXT IS AVAILABLE IN THE ALL FORMAT\*

AB WEST POINT, Pa., Oct. 4 /PRNewswire/ -- The following was released today by Merck & Co. Inc.:

#### DESCRIPTION

COMVAX(TM)\* (Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine) is a sterile bivalent vaccine made of the antigenic components used in producing PedvaxHIB(R) (Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)) and RECOMBIVAX HB(R) (Hepatitis B Vaccine (Recombinant)). These components are the *Haemophilus influenzae* type b capsular polysaccharide (PRP) that is covalently bound to an outer membrane protein complex (OMPC) of *Neisseria meningitidis* and hepatitis B surface antigen (HBsAg) from recombinant yeast cultures. *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroup B are grown in complex fermentation media.

Searcher : Shears 308-4994

The PRP is purified from the culture broth by purification procedures which include ethanol fractionation, enzyme digestion, phenol extraction and diafiltration. The OMPC from *Neisseria meningitidis* is purified by detergent extraction, ultracentrifugation, diafiltration and sterile filtration. The PRP-OMPC conjugate is prepared by the chemical coupling of the highly purified PRP (polyribosylribitol phosphate) of *Haemophilus influenzae* type b (*Haemophilus* b, Ross strain) to an OMPC of the B11 strain of *Neisseria meningitidis* serogroup B. The coupling of the PRP to the OMPC, which is necessary for enhanced immunogenicity of the PRP, is confirmed by analysis of the conjugate's components following chemical treatment which yields a unique amino acid. After conjugation, the aqueous bulk is then adsorbed onto an aluminum hydroxide adjuvant.

HBsAg is produced in recombinant yeast cells. A portion of the hepatitis B virus gene, coding for HBsAg, is cloned into yeast, and the vaccine for hepatitis B is produced from cultures of this recombinant yeast strain according to methods developed in the Merck Research Laboratories. The antigen is harvested and purified from fermentation cultures of a recombinant strain of the yeast *Saccharomyces cerevisiae* containing the gene for the adw subtype of HBsAg. The HBsAg protein is released from the yeast cells by cell disruption and purified by a series of physical and chemical methods. The vaccine contains no detectable yeast DNA but may contain not more than 1% yeast protein. The aqueous bulk is treated with formaldehyde and then adsorbed onto an aluminum hydroxide adjuvant.

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L16 ANSWER 13 OF 16 PROMT COPYRIGHT 1999 IAC

AN 92:121754 PROMT

TI Havrix launch gives SB head start

SO Pharmaceutical Business News, (7 Feb 1992) pp. N/A.

LA English

WC 792

\*FULL TEXT IS AVAILABLE IN THE ALL FORMAT\*

AB VIENNA -- The launch of Havrix, the first vaccine against Hepatitis A, has given manufacturers SmithKline Beecham Biologicals a head start into the hepatitis A market - currently estimated to be worth GBP150-GBP200 million.

The vaccine, recently launched in Switzerland and Belgium is expected to get its UK licence within a matter of weeks. Submissions have also been made in Germany, and the US application will take place mid-1992.

At a conference in Vienna, Jean Stephenne, general manager and vice-president of Rixensart (Belgium) based SmithKline Beecham Biologicals said that he expected up to three competitors to launch

Searcher : Shears 308-4994



vaccines against hepatitis A.

"We have a 12 to 18 month lead over our nearest competitor (Merck) in the European market," said Stephenne.

The Vienna conference heard infectious disease specialists outline the main target groups for the vaccine. These will be international travellers from developed countries to regions of high hepatitis A endemicity, and people working in certain "at risk occupations". The latter include staff and residents of day care centres, sewerage workers, food handlers, nursing and other health care staff, people living in military barracks or other crowded institutions, homosexuals and IV drug abusers.

Havrix is a sterile suspension of formaldehyde-inactivated hepatitis A virus (HM175 hep A strain) absorbed onto aluminium

hydroxide. Internationally the cost of the vaccine will be pitched at a similar level to SB's recently launched

hepatitis B vaccine Engerix-B, around GBP10 a dose.

A primary course of two 1 ml doses are administered one month apart. A booster one year after the initial course is expected to extend protection for up to 10 years, according to SB.

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L16 ANSWER 14 OF 16 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD

AN 94-27097 DRUGU T M S G

TI Immunogenicity of a five-component acellular pertussis vaccine in infants and young children.

AU Halperin S A; Barreto L; Friesen B; Meekison W

CS Univ.Dalhousie; Connaught-Lab.

LO Halifax, Nova Scotia, Willowdale, Ontario, Calgary, Alberta, Surrey, British Columbia, Canada

SO Arch.Pediatr.Adolesc.Med. (148, No. 5, 495-502, 1994) 3 Tab. 41 Ref.

AV Izaak Walton Killam Children's Hospital, 5850 University Ave, Halifax, Nova Scotia, Canada B3J 3G9.

LA English

DT Journal

FA AB; LA; CT

FS Literature

AN 94-27097 DRUGU T M S G

AB A study of 159 children indicated that 4- and 5-component acellular pertussis vaccines (CP4 and CP5; Connaught) were safe and immunogenic and that the 5th component, a 69-kDa membrane protein, did not increase side-effects. 137 Children were randomized to receive i.m. CP4 or CP5 alone or combined with diphtheria and tetanus toxoids (CP4DT or CP5DT, respectively) in a double-blind manner. 22 Children received i.m. CP5DT (non-blind).

Haemophilus influenzae vaccine was also administered to children receiving CP4, CP5 and CP5DT vaccines. All components of CP4 and CP5 induced Ab

Searcher : Shears 308-4994

responses. Side-effects were not significantly different between vaccines and included local reactions (tenderness, erythema, swelling and hardness) and mild/moderate systemic reactions (irritability, fever, crying, drowsiness, listlessness, pallor, reduced appetite, vomiting and diarrhea).

ABEX Methods 137 Children (aged 17-18 mth), scheduled to receive their 4th diphtheria + pertussis + tetanus vaccine, received 0.5 ml CP4 (n = 35), CP5 (n = 33), CP4DT (n = 35) or CP5DT (n = 34) followed 1 mth later by *Haemophilus influenzae* vaccine and, in the case of CP4 and CP5 recipients, DT toxoids were administered. 22 Children (aged 4-6 yr) received CP5DT. Results CP4 and CP5 (0.5-ml) contained pertussis toxin (PT; 10 ug), filamentous hemagglutinin (5 ug) and fimbriae 2 and 3 (5 ug); CP5 also contained 69-kDa protein (3 ug). CP4, CP5, CP4DT and CP5DT were adsorbed to aluminum phosphate (1.5 mg) and contained 0.6% 2-phenoxyethanol as preservative. Local reactions (mainly tenderness) occurred in 8.6-29.4% of 17-18 mth-old children and 71.4% of 4-6 yr-old children; 1 child in the latter group had a swelling of 70 mm but no younger child had a swelling over 35 mm. Systemic reactions (mainly irritability) occurred in 40-65.7% of 17-18 mth-old children and 38.1% of 4-6 yr-old children; fever/feverishness occurred in 20% but no temperature was above 39 deg. Local and systemic reactions were more frequent with CP5 and CP5DT but this did not achieve significance. Ab responses were mainly IgG. Ab response to PT was less than expected in all groups; 55-66% had at least 4-fold increase in PT-neutralizing titer (Chinese hamster ovary cell cytotoxicity) and 88-100% had a similar increase by ELISA. Previous doses had been Canadian whole-cell vaccine, thus, this represented the 1st exposure to PT. Ab response to the 69-kDa protein was marked in CP5 recipients but slight increase was observed in CP4 recipients. (W2/KP)

L16 ANSWER 15 OF 16 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD  
 AN 90-19710 DRUGU M  
 TI Opsonophagocidal Activity in Sera from Infants and Children  
 Immunized with *Haemophilus influenzae*  
 Type b Conjugate Vaccine (Meningococcal Protein  
 Conjugate).  
 AU Gray B M  
 LO Birmingham, Alabama, United States  
 SO Pediatrics (85, No. 4, Pt. 2, 694-97, 1990) 1 Fig. 1 Tab. 17 Ref.  
 CODEN: PEDIAU ISSN: 0031-4005  
 AV Department of Pediatrics, University of Alabama at Birmingham,  
 Birmingham, AL 35294, U.S.A.  
 LA English  
 DT Journal  
 FA AB; LA; CT

Searcher : Shears 308-4994

09/210995

FS Literature

AN 90-19710 DRUGU M

AB I.m. administration of 1 or 2 doses of

*Haemophilus influenzae* type b capsular polysaccharide (polyribosylribitol phosphate, PRP) conjugated to an outer membrane protein complex (OMPC) from *Neisseria meningitidis* group B (PedvaxHIB) to 97 children aged 2-18+ mth resulted in excellent antibody responses and promotion of opsonophagocidal activity in sera, even in the youngest age group. 3 Different vaccine lots, 1072, 1080 and 1085 induced similar antibody and immune responses. Overall, 94% of vaccinees

responded as measured using RIA of the anti-PRP antibody levels in sera, and functional measurements of opsonophagocidal activity.

ABEX Methods 3 Different lots of vaccine, 1072, 1080 and 1085 were administered i.m. at 15 ug after being adsorbed to aluminum hydroxide. Children 12 mth and older received a single dose, while those younger than 18 mth received 2 doses with a 2 mth interval. Results Nearly all sera obtained from the 97 participants prior to vaccination had RIA antibody levels of less than 1 ug/ml, and opsonophagocidal activity of less than 50% killing of the inoculum. Sera obtained after the 1st dose of vaccine generally had over 1 ug/ml of antibody, and opsonophagocidal activity over 50% in 90% of vaccinees. There appeared to be an all-or-nothing effect in the opsonophagocytic test. There were no significant differences in the response elicited by the 3 different vaccine lots. Responses were greater among children older than 18 mth, and least in those younger than 6 mth. Nevertheless, 80% of the youngest infants had anti-PRP antibody levels in excess of 1 ug/ml and had opsonophagocidal activity. 3 Infants less than 12 mth old had anti-PRP levels just below the cut-off value. All 3 responded well to the 2nd dose leaving only 2 infants in that age group who failed to respond with levels of 1 ug/ml after receiving the 2nd dose of vaccine. 2 Children in each of the older age groups failed to respond after a single dose of vaccine. Thus 94% of vaccinees responded with antibody as measured by the RIA and functional methods. (B27/LPD)

L16 ANSWER 16 OF 16 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD

AN 88-21442 DRUGU T M S

TI Bacterial Vaccines for Splenectomized Patients.

AU Kafidi K T; Rotschafer J C

LO St. Paul, Minnesota, United States

SO Drug Intell.Clin.Pharm. (22, No. 3, 192-97, 1988) 1 Tab. 65 Ref.

CODEN: DICPBB

AV College of Pharmacy, University of Minnesota and Department of Clinical Pharmacy, St. Paul-Ramsey Medical Center, 640 Jackson St., St. Paul, MN 55101, U.S.A.

LA English

Searcher : Shears 308-4994

09/210995

DT Journal  
FA AB; LA; CT  
FS Literature

AN 88-21442 DRUGU T M S

AB Asplenic persons are at increased risk of serious bacterial infection, particularly due to Strept. pneumoniae, Hemophilus influenzae and Neisseria meningitidis.

Vaccines that are available for these common pathogens are reviewed. None is 100% effective, and the concept of ongoing antibiotic cover is discussed. The safety profiles of the currently available vaccines weigh heavily in favor of routine vaccination. Recommendations for the use of these vaccines are given.

ABEX Strept. pneumoniae is responsible for about 50% of post-splenectomy infections, but Hemophilus influenzae and Neisseria meningitidis are also important pathogens. Mortality can be as high as 50-80% despite prompt antibiotic therapy. Strept. pneumoniae vaccine recommendations are outlined, and include patients aged over 65, asplenic patients, and patients with immunodeficiency syndromes. The new 23-valent vaccine is about 85% effective in asplenic patients over 15 yr old. Protection lasts about 2 yr, and vaccination may be more effective if administered prior to splenectomy. Adverse reactions include fever, erythema, pain and swelling, and severe localized and systemic reactions may occur with booster doses. Penicillin V prophylaxis is recommended along with the vaccination, and erythromycin may be employed in patients with penicillin intolerance. 2 Different types of hemophilus type B vaccine exist currently with 1 being conjugated to diphtheria toxoid, and recommendations as to their use are based on studies in children. The conjugate vaccine is more immunogenic than the polysaccharide vaccine, and can be used in younger children, and tolerance is good. Rifampicin prophylaxis is mentioned. Neisseria meningitidis vaccine is available in a tetravalent lyophilized form, and adjuvants include aluminum phosphate. Adverse effects include localized erythema and transient fever. (B27/LPD) (J.C.R.)

(FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, LIFESCI, BIOTECHDS, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, PROMT, TOXLIT, TOXLINE, DRUGU, DRUGNL, DRUGB, DRUGLAUNCH' ENTERED AT 12:57:07 ON 25 MAR 1999)

L17 306 S LOOSMORE S?/AU  
L18 21447 S YANG Y?/AU  
L19 1208 S CHONG P?/AU  
L20 12005 S KLEIN M?/AU  
L21 42 S L17 AND L18 AND L19 AND L20  
L22 236 S L17 AND (L18 OR L19 OR L20)  
L23 147 S L18 AND (L19 OR L20)

Searcher : Shears 308-4994

Author (S)

09/210995

L24 284 S L19 AND L20  
L25 34299 S L17 OR L18 OR L19 OR L20  
L26 252 S (L21 OR L22 OR L23 OR L24 OR L25) AND L1  
L27 97 DUP REM L26 (155 DUPLICATES REMOVED)  
L28 11 S L27 AND ADMIN?

=> d 1-11 bib abs

L28 ANSWER 1 OF 11 CAPLUS COPYRIGHT 1999 ACS  
AN 1998:414012 CAPLUS  
DN 129:174401  
TI A 20-kilodalton N-terminal fragment of the D15 protein contains a protective epitope(s) against *Haemophilus influenzae* type a and type b  
AU Yang, Yan-Ping; Thomas, Wayne R.; Chong, Pele; Loosmore, Sheena M.; Klein, Michel H.  
CS Research Center, Pasteur Merieux Connaught Canada, North York, ON, M2R 3T4, Can.  
SO Infect. Immun. (1998), 66(7), 3349-3354  
CODEN: INFIBR; ISSN: 0019-9567  
PB American Society for Microbiology  
DT Journal  
LA English  
AB A conserved 80-kDa minor outer membrane protein, D15, of *H. influenzae* has been shown to be a protective antigen in lab. animals against *H. influenzae* type a (Hia) or type b (Hib) infection. To localize the protective B-cell epitope(s) within the D15 protein and to further explore the possibility of using synthetic peptides as vaccine antigens, a 20-kDa N-terminal fragment of D15 protein [truncated D15 (tD15)] was expressed as a fusion protein with glutathione S-transferase in *Escherichia coli*. The tD15 moiety was cleaved from glutathione S-transferase by using thrombin and purified to homogeneity. The purified sol. tD15 appeared to contain immunodominant protective epitope(s) against Hia and Hib, since rabbit antisera directed against tD15 were capable of protecting infant rats from Hia or Hib bacteremia. The ease of purifn. of sol. tD15, therefore, makes it a better candidate antigen than the full-length recombinant D15 which is produced as inclusion bodies in *E. coli*. Furthermore, both the purified tD15 fragment and a mixt. of tD15-derived peptides spanning amino acid residues 93 to 209 of the mature D15 protein were capable of inhibiting the protection against Hib conferred on infant rats by rabbit anti-tD15 antiserum, indicating that the protective epitopes of D15 may not be conformational. However, the administration of pooled rabbit immune sera raised against the same panel of peptides failed to protect infant rats from Hib infection.

L28 ANSWER 2 OF 11 CAPLUS COPYRIGHT 1999 ACS  
Searcher : Shears 308-4994

AN 1997:560572 CAPLUS  
 DN 127:233288  
 TI Effect of lipid modification on the physicochemical, structural, antigenic and immunoprotective properties of *Haemophilus influenzae* outer membrane protein P6  
 AU Yang, Yan-Ping; Munson, Robert S., Jr; Grass, Susan; Chong, Pele; Harkness, Robin E.; Gisonni, Lucy; James, Olive; Kwok, Yan; Klein, Michel H.  
 CS Research Center, Pasteur Merieux, Connaught, Canada, North York, M2R 3T4, Can.  
 SO Vaccine (1997), 15(9), 976-987  
 CODEN: VACCDE; ISSN: 0264-410X  
 PB Elsevier  
 DT Journal  
 LA English  
 AB The outer membrane lipoprotein, P6 of *H. influenzae* was studied to det. the importance of the native palmitoyl moiety on its physicochem. and immunol. properties. A recombinant P6 (rP6) mol. devoid of lipidation signal sequence was expressed in *Escherichia coli* and its properties were compared to those of the palmitoylated protein purified from *H. influenzae*. The isoelec. point of rP6 was more acidic than that of the native protein and also exhibited less secondary structure than P6 as judged by CD. However, both forms of P6 induced identical P6-specific antibody titers in guinea pigs when Freund's adjuvant was used. These antisera reacted with a panel of overlapping P6 peptides in a comparable manner and in addn., rabbit antisera raised against the P6 peptides reacted equally well with P6 and rP6. Furthermore, all human convalescent sera tested exhibited similar anti-P6 and anti-rP6 antibody titers. However, rP6 was less immunogenic than P6 when administered either without adjuvant or in alum and when tested in competitive inhibition studies with anti-P6 antibodies, was a less effective inhibitor than native P6, suggesting a diminution in some of the antigenic activity of rP6. In spite of these differences, rP6 was capable of eliciting a protective antibody response against live *H. influenzae* type b challenge in a modified infant rat model of bacteremia. Thus, the non-fatty acylated rP6 could possibly be substituted for native P6 in a vaccine against *H. influenzae*.

L28 ANSWER 3 OF 11 CAPLUS COPYRIGHT 1999 ACS  
 AN 1997:463653 CAPLUS  
 DN 127:113174  
 TI Immunogenicity of *Haemophilus influenzae* proteins encapsulated within biodegradable microparticles  
 AU Sokoll, Ken; Pszczolko, Helena; Frank, Peter; Hu, Jian; Yang, Yan-Ping; Chong, Pele; Klein, Michel  
 CS Research Centre, Pasteur Merieux Connaught Canada, Willowdale, ON,  
 Searcher : Shears 308-4994

09/210995

SO M2R 3T4, Can.  
Proc. Int. Symp. Controlled Release Bioact. Mater. (1997), 24th,  
421-422  
CODEN: PCRMEY; ISSN: 1022-0178  
PB Controlled Release Society, Inc.  
DT Journal  
LA English  
AB The humoral response to terpolymer (PLGpZS and PLGpS)-  
microencapsulated Hin-47 (*Haemophilus influenzae*  
proteins) can be substantially increased when administered  
via parenteral or mucosal routes. The quality of the immunogenic  
response (presentation of antigen) is influenced as indicated by  
differences with the IgG subtypes elicited. Mucosal immunization  
with antigen encapsulated microparticles has been shown to elicit  
moderate levels of sIgA. This has implications for the use of  
microparticles-based delivery systems for the induction of local  
protection at mucosal surfaces, as this is most often assocd. with  
sIgA in local secretions.

L28 ANSWER 4 OF 11 CAPLUS COPYRIGHT 1999 ACS  
AN 1997:18360 CAPLUS  
DN 126:46316  
TI Cloning and expression of 200 kilodalton outer membrane protein gene  
of *Moraxella catarrhalis* and vaccines for otitis  
media  
IN Sasaki, Ken; Harkness, Robin E.; Loosmore, Sheena M.;  
Chong, Pele; Klein, Michel H.  
PA Connaught Laboratories Limited, Can.; Sasaki, Ken; Harkness, Robin  
E.; Loosmore, Sheena M.; Chong, Pele; Klein, Michel, H.  
SO PCT Int. Appl., 109 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9634960	A1	19961107	WO 96-CA264	19960429
	W:	AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI			
	RW:	KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN			
	US 5808024	A	19980915	US 95-478370	19950607
	AU 9653941	A1	19961121	AU 96-53941	19960429
	EP 826052	A1	19980304	EP 96-910872	19960429
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI			

Searcher : Shears 308-4994

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JP 11502415      T2    19990302      JP 96-532876      19960429  
PRAI US 95-431718    19950501  
US 95-478370    19950607  
US 96-621944    19960326  
WO 96-CA264    19960429

AB An isolated and purified outer membrane protein (OMP) of a Moraxella strain, particularly M. catarrhalis, having a mol. mass of about 200 kDa, is provided. The about 200 kDa OMP as well as nucleic acid mols. encoding the same are useful in diagnostic applications and immunogenic compns., particularly for in vivo administration to a host to confer protection against disease caused by a bacterial pathogen that produces the about 200 kDa OMP or produces a protein capable of inducing antibodies in a host specifically reactive with the about 200 kDa OMP. The gene for the OMP was cloned and sequenced. The 200 kDa OMP was almost always present in Moraxella strains isolated from patients suffering from otitis media. Antibodies specific for this protein were identified in serum from a convalescent patient having recovered from otitis media due to M. catarrhalis. Immunization of guinea pigs with an internal fragment of this protein generated antibodies which recognizes the 200 kDa protein.

L28 ANSWER 5 OF 11 CAPLUS COPYRIGHT 1999 ACS

AN 1996:137694 CAPLUS

DN 124:173429

TI Adjuvant compositions comprising a mineral salt and another immunostimulating compound

IN Kandil, Ali; James, Olive A.; Chong, Pele; Klein, Michel H.

PA Cannaught Laboratories Ltd., Can.

SO PCT Int. Appl., 54 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9534308	A2	19951221	WO 95-CA359	19950615
	WO 9534308	A3	19960523		

W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN

RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

US 5837250	A	19981117	US 95-483856	19950607
CA 2192659	AA	19951221	CA 95-2192659	19950615
AU 9526670	A1	19960105	AU 95-26670	19950615

Searcher : Shears 308-4994



09/210995

EP 765163                    A2    19970402                    EP 95-921672                    19950615  
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL,  
PT, SE

PRAI US 94-261194                    19940616  
WO 95-CA359                    19950615

OS    MARPAT 124:173429

AB    Adjuvant compns. for modulating an immune response to an antigen administered to a host comprise a mineral salt adjuvant and at least one other adjuvant. The compns. provide an adjuvanting effect on an antigen which is greater than the adjuvanting effect attainable by one of the adjuvants alone. An antigen is covalently bonded to a glycolipid analog to provide a discrete mol. which exhibits an enhanced adjuvanting effect on the antigen which is greater than the adjuvanting effect attainable in the absence of such covalent bonding. The antigen is microbial pathogens, bacteria, viruses, proteins, glycoproteins, lipoproteins, peptides, glycopeptides, toxoids, carbohydrates, tumor-specific antigens, etc. In example, synthetic peptides were prepd. as antigen, and N-(2-L-leucine-amino-2-deoxy-.beta.-D-glucopyranosyl)-N-octadecyldodecanamide acetate, tripalmityl-Cys-Ser-Ser-Asn-Ala, tripalmityl-Cys-Ser-Glu-Glu-Glu-Glu, tripalmityl-Cys-Ser-Lys-Lys-Lys-Lys, etc. were prepd. as adjuvant. Formulations contg. these synthetic antigen and adjuvants were prepd. as vaccines for HIV, flu, RSV, PIV3, flu BHA, pertussis toxoid, etc.

L28    ANSWER 6 OF 11    MEDLINE

AN    1998453011                    MEDLINE

DN    98453011

TI    Study on *Haemophilus influenzae* type b diseases in China: the past, present and future.

AU    Yang Y; Shen X; Jiang Z; Liu X; Leng Z; Lu D; Rao J; Liu J; Chang L

CS    Laboratory of Microbiology and Immunology, Beijing Children's Hospital, China.

SO    PEDIATRIC INFECTIOUS DISEASE JOURNAL, (1998 Sep) 17 (9 Suppl) S159-65.

Journal code: OXJ. ISSN: 0891-3668.

CY    United States

DT    Journal; Article; (JOURNAL ARTICLE)

LA    English

FS    Priority Journals

EM    199902

EW    19990204

AB    Meningitis caused by *Haemophilus influenzae* type b (Hib) is a common and serious disease for which there now are WHO-certified vaccines that are recommended for universal infant immunization in North America and European countries. If these vaccines are to be recommended in Asia, it is necessary to know the incidence, age distribution and clinical outcome of Hib meningitis

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and other systemic infections in this region. Data on Hib disease in China are scanty. Hib meningitis was common during the 1950s in China, accounting for up to 16% of all of pyogenic meningitis (up to 38% of cases were caused by unknown pathogens), despite severe epidemics of meningococcal meningitis during that period. Since 1989 we have conducted hospital- and community-based etiologic and epidemiologic studies of bacterial meningitis. Hib accounts for 30 to 50% of bacterial meningitis in China. The incidence of Hib meningitis in Hefei City was 10.4 per 100000 children <5 years, a result relatively lower than in the West but higher than the rate of 2.7 found in a retrospective study in Hong Kong. Pneumonia is the primary cause of death for Chinese children. From 1991 to 1993 the average mortality of children <5 years because of pneumonia was 1563.2 per 100000. To achieve the goal of reducing the death rate of children by one-third by the year 2000, greater efforts should be made to reduce the mortality of children with pneumonia. Our preliminary study showed that about one-fourth to one-third of cases of pneumonia in Chinese children might be caused by Hib. Therefore Hib vaccination for infants and children in China might be an effective and valuable procedure to achieve the goal.

L28 ANSWER 7 OF 11 MEDLINE

AN 95312349 MEDLINE

DN 95312349

TI Multicenter trial of cefpodoxime proxetil vs. amoxicillin-clavulanate in acute lower respiratory tract infections in childhood. International Study Group.

AU Klein M

CS Department of Paediatrics and Child Health, University of Cape Town, South Africa.

SO PEDIATRIC INFECTIOUS DISEASE JOURNAL, (1995 Apr) 14 (4 Suppl) S19-22.

Journal code: OXJ. ISSN: 0891-3668.

CY United States

DT (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)

(MULTICENTER STUDY)

(RANDOMIZED CONTROLLED TRIAL)

LA English

FS Priority Journals

EM 199509

AB Acute lower respiratory tract infections in children are a worldwide public health problem, with an estimated 4 million potentially preventable deaths every year. Until recently, penicillin and related drugs were the treatment of choice for empiric therapy of paediatric lower respiratory tract infections. However, concerns over the emergence of penicillin-resistant strains of Streptococcus pneumoniae and beta-lactamase-producing strains of Haemophilus influenzae and Moraxella catarrhalis

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have led physicians to turn increasingly towards alternatives, such as the third generation cephalosporins. The oral extended spectrum cephalosporin cefpodoxime proxetil is highly active against the bacterial pathogens commonly associated with childhood lower respiratory tract infections. In order to evaluate its clinical efficacy in children with acute febrile lower respiratory tract infections, an international, multicenter, comparative, randomized open study was conducted in children ages 3 months to 11.5 years. Of 348 cases enrolled, 234 were randomized to cefpodoxime proxetil (8 mg/kg/day twice daily) and 114 to amoxicillin/clavulanate (amoxicillin 40 mg/kg/day 3 times a day). The duration of treatment was 10 days. Pretreatment diagnosis was pneumonia in 292 patients, bronchiolitis in 19 patients and acute bronchitis in 37 patients. Pathogens isolated from 59 cases included *H. influenzae* (47.5%), *S. pneumoniae* (23.7%), *M. catarrhalis* (11.9%) and *Haemophilus parainfluenzae* (6.8%). Clinical efficacy was evaluable in 278 children at the end of treatment when 95.2% of patients in the cefpodoxime proxetil group and 96.7% of patients in the amoxicillin/clavulanate group showed a satisfactory clinical response (cured or improved). The improvement was sustained at the follow-up visit, 10 to 20 days after completion of treatment. (ABSTRACT TRUNCATED AT 250 WORDS)

L28 ANSWER 8 OF 11 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.  
 AN 95121497 EMBASE  
 DN 1995121497  
 TI Multicenter trial of cefpodoxime proxetil vs. amoxicillin-clavulanate in acute lower respiratory tract infections in childhood.  
 AU Klein M.  
 CS Dept. of Paediatrics/Child Health, University of Cape Town, Red Cross War Memorial Child. Hosp., Klipfontein Road, 7700 Rondebosch, South Africa  
 SO Pediatric Infectious Disease Journal, (1995) 14/4 SUPPL. I (S19-S22).  
 ISSN: 0891-3668 CODEN: PIDJEV  
 CY United States  
 DT Journal; Conference Article  
 FS 007 Pediatrics and Pediatric Surgery  
 037 Drug Literature Index  
 LA English  
 SL English  
 AB Acute lower respiratory tract infections in children are a worldwide public health problem, with an estimated 4 million potentially preventable deaths every year. Until recently, penicillin and related drugs were the treatment of choice for empiric therapy of paediatric lower respiratory tract infections. However, concerns over the emergence of penicillin-resistant strains of *Streptococcus pneumoniae* and beta-lactamase-producing strains of

Searcher : Shears 308-4994

*Haemophilus influenzae* and *Moraxella catarrhalis* have led physicians to turn increasingly towards alternatives, such as the third generation cephalosporins. The oral extended spectrum cephalosporin cefpodoxime proxetil is highly active against the bacterial pathogens commonly associated with childhood lower respiratory tract infections. In order to evaluate its clinical efficacy in children with acute febrile lower respiratory tract infections, an international, multicenter, comparative, randomized open study was conducted in children ages 3 months to 11.5 years. Of 348 cases enrolled, 234 were randomized to cefpodoxime proxetil (8 mg/kg/day twice daily) and 114 to amoxicillin/clavulanate (amoxicillin 40 mg/kg/day 3 times a day). The duration of treatment was 10 days. Pretreatment diagnosis was pneumonia in 292 patients, bronchiolitis in 19 patients and acute bronchitis in 37 patients. Pathogens isolated from 59 cases included *H. influenzae* (47.5%), *S. pneumoniae* (23.7%), *M. catarrhalis* (11.9%) and *Haemophilus parainfluenzae* (6.8%). Clinical efficacy was evaluable in 278 children at the end of treatment when 95.2% of patients in the cefpodoxime proxetil group and 96.7% of patients in the amoxicillin/clavulanate group showed a satisfactory clinical response (cured or improved). The improvement was sustained at the follow-up visit, 10 to 20 days after completion of treatment. There was no difference in bacteriologic efficacy of the two treatments, and both drugs were well-tolerated. Thus cefpodoxime proxetil is highly effective and well tolerated in childhood pneumonia and is at least as effective as the comparator drug.

L28 ANSWER 9 OF 11 BIOTECHDS COPYRIGHT 1999 DERWENT INFORMATION LTD  
 AN 97-06952 BIOTECHDS  
 TI New non-denatured transferrin receptor protein from *Moraxella* and related antibodies;  
     *Moraxella catarrhalis* transferrin receptor monoclonal antibody production and hybridoma cell culture construction  
 AU Yang Y P; Myers L E; Harkness R E; Klein M H  
 PA Connaught-Lab.  
 LO North York, Ontario, Canada.  
 PI WO 9713785 17 Apr 1997  
 AI WO 96-CA684 11 Oct 1996  
 PRAI US 95-540753 11 Oct 1995  
 DT Patent  
 LA English  
 OS WPI: 97-235839 [21]  
 AN 97-06952 BIOTECHDS  
 AB An isolated and purified non-denatured transferrin receptor protein of a *Moraxella* strain (preferably *Moraxella catarrhalis* and especially *M. catarrhalis* 4223, 5191 or 135) having an apparent mol.wt. of about 80,000-90,000 as determined by SDS-PAGE, a fragment or an analog is claimed. Also claimed are antibodies raised against the transferrin receptor. A method (claimed) for  
     Searcher : Shears 308-4994

producing monoclonal antibodies specific for the transferrin receptor involves: (a) administering the transferrin receptor protein to at least one mouse to produce at least one immunized mice; (b) removing B-lymphocytes from at least one immunized mouse; (c) fusing the B-lymphocytes from the immunized mouse with myeloma cells, thereby producing hybridomas; (d) cloning the hybridomas; (e) selecting the clones which produce anti-transferrin receptor protein antibody; (f) culturing the anti-transferrin receptor protein antibody-producing clone; and (g) isolating anti-transferrin receptor protein antibodies from the cultures. The antibodies may be used in the diagnostic detection of the transferrin receptor, e.g. to differentiate *Moraxella* sp. from other bacteria that cause otitis media.

(57pp)

- L28 ANSWER 10 OF 11 SCISEARCH COPYRIGHT 1999 ISI (R)  
 AN 94:11260 SCISEARCH  
 GA The Genuine Article (R) Number: MM453  
 TI BRANHAMMELLA-CATARRHALIS PATHOGENESIS IN SCID AND SCID/BEIGE MICE  
 AU HARKNESS R E; GUIMOND M J; MCBEY B A; KLEIN M H; PERCY D  
 H; CROY B A (Reprint)  
 CS UNIV GUELPH, ONTARIO VET COLL, DEPT BIOMED SCI, GUELPH N1G 2W1, ON, CANADA (Reprint); UNIV GUELPH, ONTARIO VET COLL, DEPT BIOMED SCI, GUELPH N1G 2W1, ON, CANADA; UNIV GUELPH, ONTARIO VET COLL, DEPT PATHOL, GUELPH N1G 2W1, ON, CANADA; CONNAUGHT CTR BIOTECHNOL RES, N YORK, ON, CANADA  
 CYA CANADA  
 SO APMIS, (OCT 1993) Vol. 101, No. 10, pp. 805-810.  
 ISSN: 0903-4641.  
 DT Note; Journal  
 FS LIFE  
 LA ENGLISH  
 REC Reference Count: 25  
 \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*  
 AB SCID and SCID/beige mice were used to study the pathogenesis of *B. catarrhalis* administered by intranasal, intraperitoneal or intravenous routes. Challenged adult animals did not appear overtly clinically ill. Similar symptoms were observed regardless of the challenge route, and pretreatment of mice with human transferrin did not enhance clinical virulence. Susceptibility to *B. catarrhalis* appeared to be age-dependent as some mice under one week of age died following challenge. Postmortem findings included circumscribed pale foci on the liver, splenomegaly and mineralization of the myocardium. Presence of lesions did not correlate with the assessment of clinical well being, and severity of the lesions was found to be challenge strain-dependent. Liver lesions and splenomegaly were not observed in animals challenged with heat-killed bacteria or placebo. SCID/beige mice were more affected than SCID mice both clinically and pathologically, suggesting that

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natural killer cell and polymorphonuclear cell functions may be important in resolving *B. catarrhalis* challenge.

L28 ANSWER 11 OF 11 TOXLINE

AN 1995:286714 TOXLINE

DN TOXBIB-95-312349

TI Multicenter trial of cefpodoxime proxetil vs. amoxicillin-clavulanate in acute lower respiratory tract infections in childhood. International Study Group.

AU Klein M

CS Department of Paediatrics and Child Health, University of Cape Town, South Africa.

SO PEDIATRIC INFECTIOUS DISEASE JOURNAL, (1995): Vol. 14, No. 4 SUPPL, PS19-22.

Journal code: OXJ. ISSN: 0891-3668.

DT (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)

(MULTICENTER STUDY)

(RANDOMIZED CONTROLLED TRIAL)

FS TOXBIB

LA English

OS MEDLINE 95312349

EM 199509

AB Acute lower respiratory tract infections in children are a worldwide public health problem, with an estimated 4 million potentially preventable deaths every year. Until recently, penicillin and related drugs were the treatment of choice for empiric therapy of paediatric lower respiratory tract infections. However, concerns over the emergence of penicillin-resistant strains of *Streptococcus pneumoniae* and beta-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella catarrhalis* have led physicians to turn increasingly towards alternatives, such as the third generation cephalosporins. The oral extended spectrum cephalosporin cefpodoxime proxetil is highly active against the bacterial pathogens commonly associated with childhood lower respiratory tract infections. In order to evaluate its clinical efficacy in children with acute febrile lower respiratory tract infections, an international, multicenter, comparative, randomized open study was conducted in children ages 3 months to 11.5 years. Of 348 cases enrolled, 234 were randomized to cefpodoxime proxetil (8 mg/kg/day twice daily) and 114 to amoxicillin/clavulanate (amoxicillin 40 mg/kg/day 3 times a day). The duration of treatment was 10 days. Pretreatment diagnosis was pneumonia in 292 patients, bronchiolitis in 19 patients and acute bronchitis in 37 patients. Pathogens isolated from 59 cases included *H. influenzae* (47.5%), *S. pneumoniae* (23.7%), *M. catarrhalis* (11.9%) and *Haemophilus parainfluenzae* (6.8%). Clinical efficacy was evaluable in 278 children at the end of treatment when 95.2% of patients in the cefpodoxime proxetil group and 96.7% of patients in

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09/210995

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